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THIRTY-FIFTH ANNUAL SESSION—CHICAGO, ILL., APRIL 5–9, 1954

A DIGEST AND EVALUATION OF THE VAST EXPERIENCE OF THE MAYO CLINIC DURING THE PAST TEN YEARS IN THE DIAGNOSIS AND TREATMENT OF A SERIES OF MORE THAN 30,000 VERIFIED PRIMARY AND POSTOPERATIVE RECURRENT PEPTIC ULCERS RANGING FROM THE ESOPHAGUS TO THE ILEUM.

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And ANDREW B. RIVERS, M.D., F.A.C.P., Late Associate Professor of Medicine, Mayo Foundation; Consultant Division of Medicine, Mayo Clinic

With FOREWORD by GEORGE B. HUSTERIAN, M.D.
and CONTRIBUTIONS by HERBERT W. SCHMIDT, M.D., C. ALLEN GOOD, M.D., and RICHARD R. PERATTONI, M.D.

A RECENT ESTIMATE PLACES THE INCIDENCE OF PEPTIC ULCER AT 5% OF OUR POPULATION, INDICATING ALMOST 8 MILLION CASES IN THE U.S.A. WITH AN ANNUAL INCREASE OF ABOUT 150,000 NEW CASES WHICH WILL DEVELOP IN PERSONS OVER AGE 30.

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- Indications for surgical treatment are based upon the clinical interpretation of pain patterns, the location of the ulcer and its complications.
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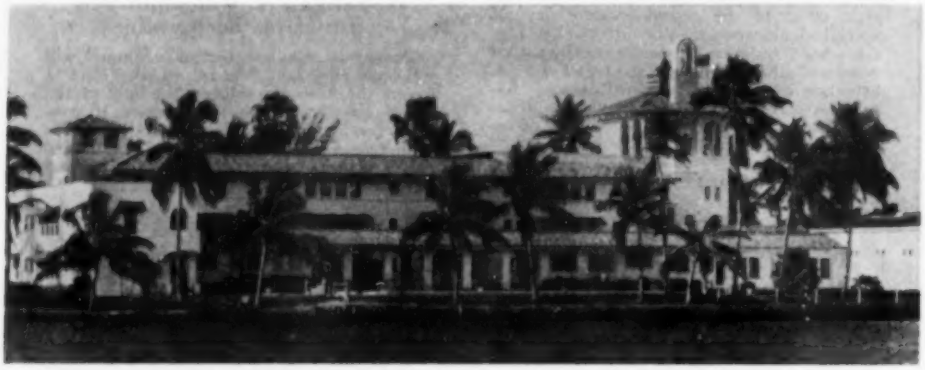

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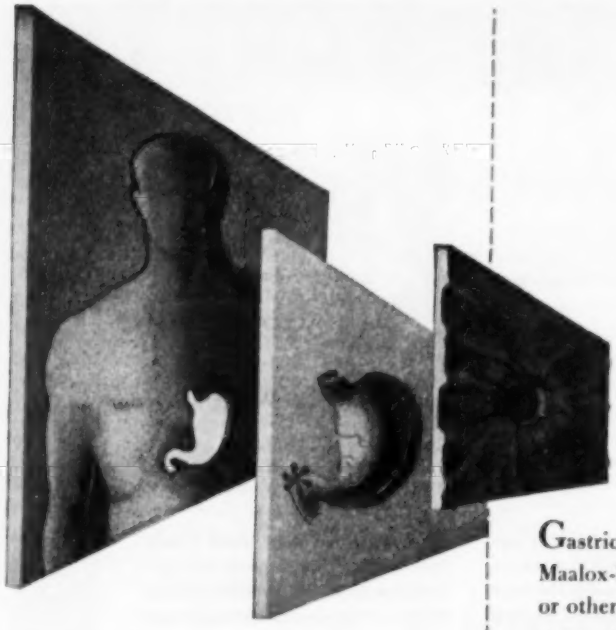

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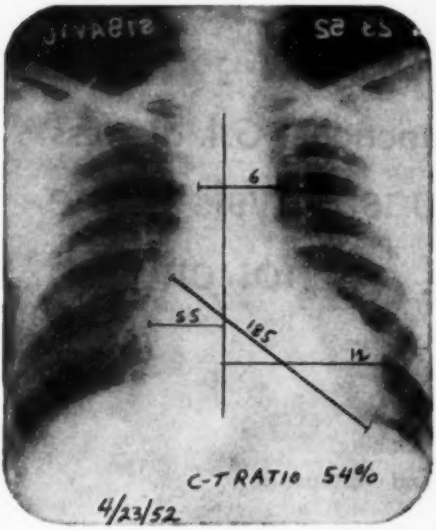

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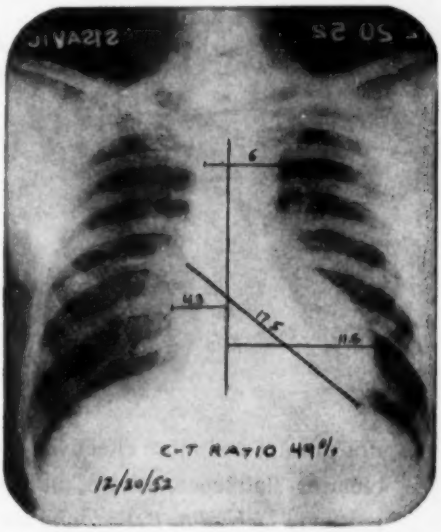

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1. Kuhn, P. H.: Angiology *4*:195 (June) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.
3. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.

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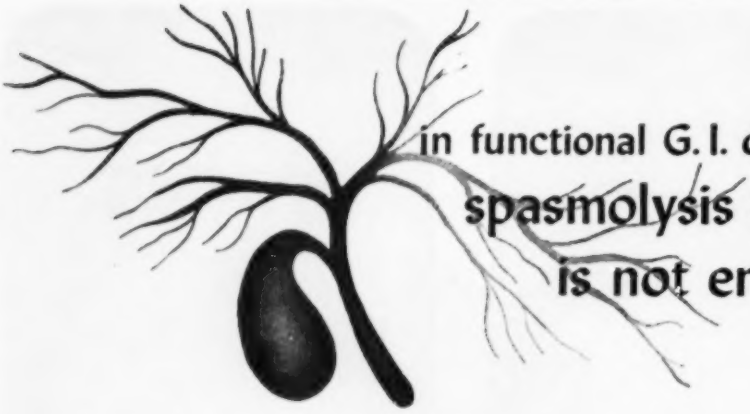

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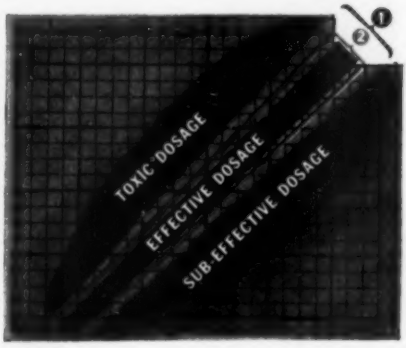

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1. Cathie, I.A.B., and Mac Farlane, J.C.W.: Brit. M.J. 1:805 (April 13) 1953
2. Berkowitz, B.: Antibiotics and Chemotherapy 5:618 (June) 1953
3. New and Nonofficial Remedies, J.B. Lippincott Co., Philadelphia, 1950

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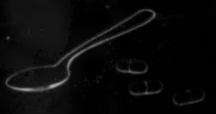

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EMORY UNIVERSITY SCHOOL OF MEDICINE

A comprehensive course to be given February 8–12, 1954, and designed for those with previous experience in electrocardiography. Emphasis will be placed on the electrophysical factors involved and on the vector methods of interpreting the electrocardiograph.

Faculty from Emory University School of Medicine

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DR. J. WILLIS HURST
DR. BERNARD S. LIPMAN
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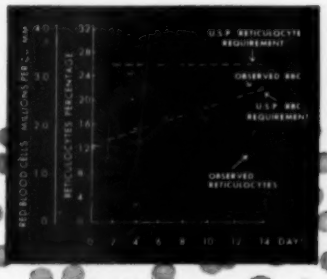

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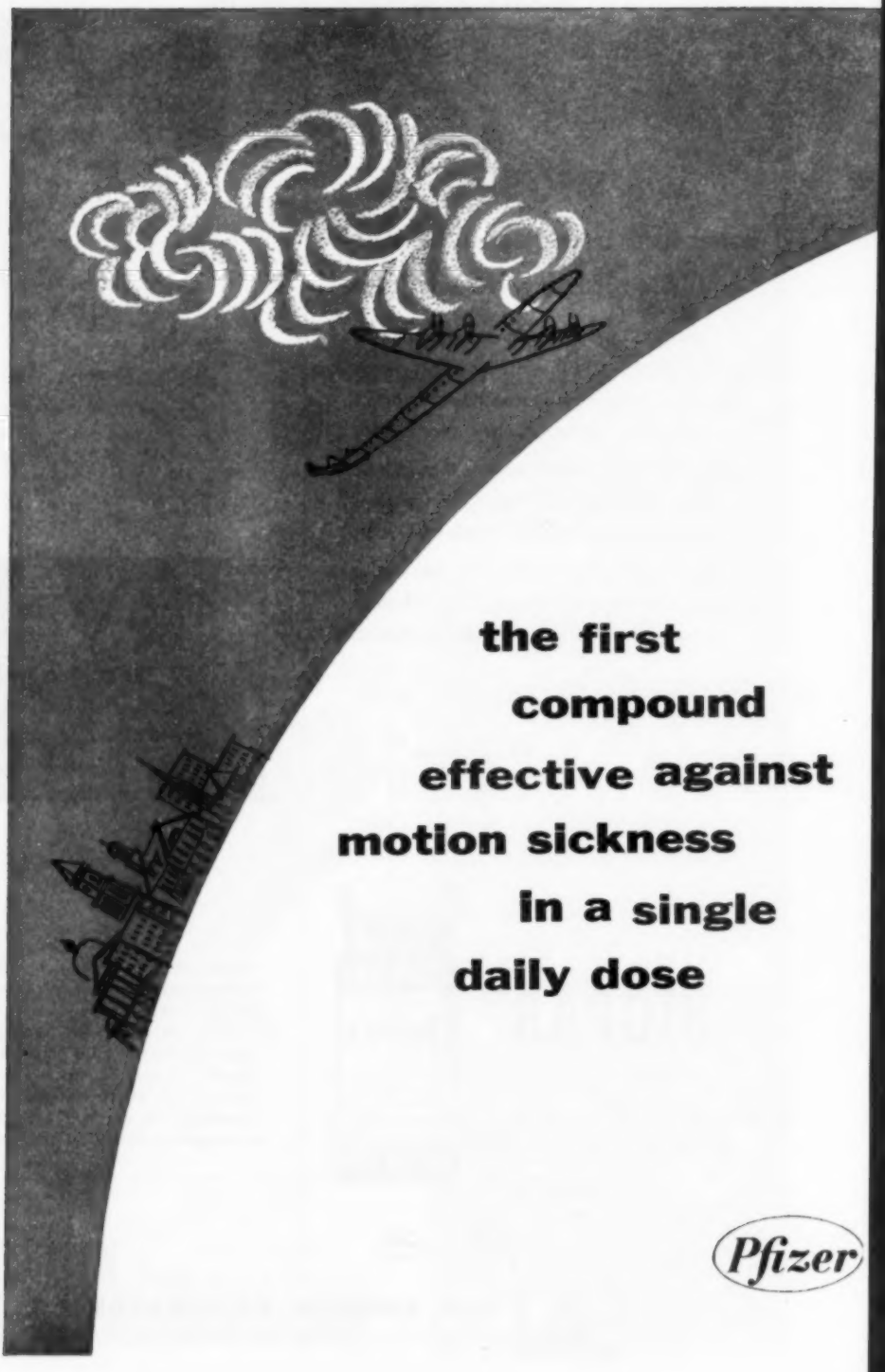
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1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

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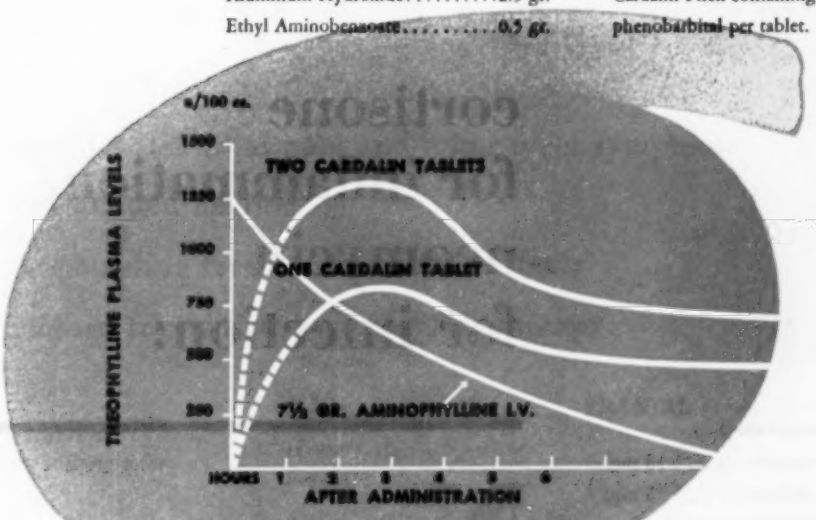
Supplied: Bottles of 50, 100, 500, 1000. Also available, Cardalin-Phen containing ¼ gr. phenobarbital per tablet.



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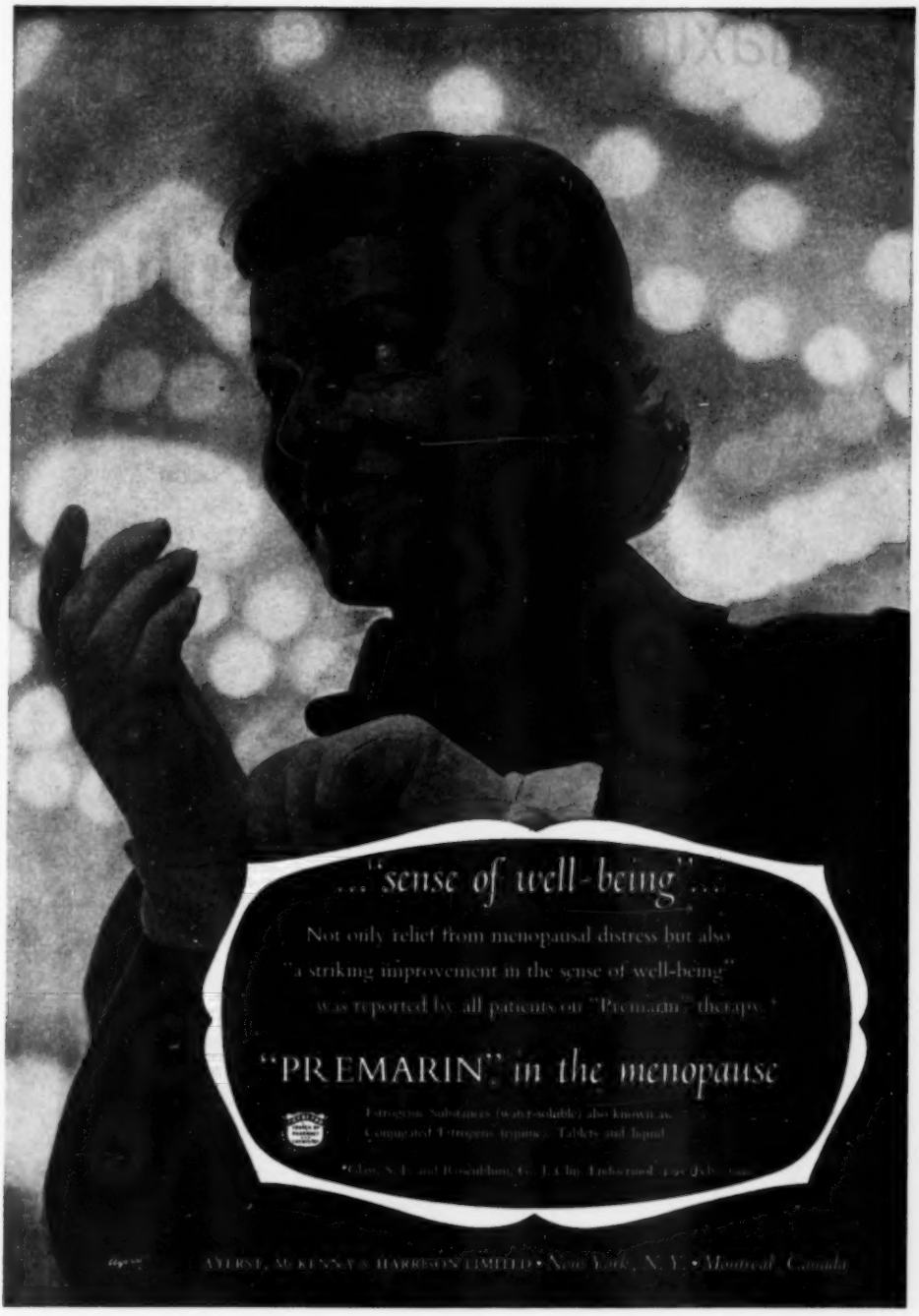
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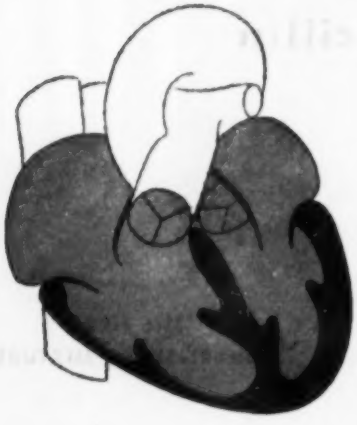

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*Strauss, V.; Simon, D. L.; Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent, Am. Heart J. 44:787, 1952.

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Nicotinamide	30 mg.
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Vitamin B_{12} (as vitamin B_{12} concentrate)	2 mcg.
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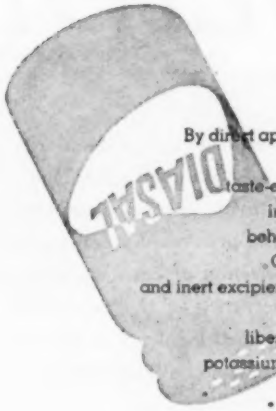

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1. Zimmerman, A. B., and others: A Comparative Study of Sodium-free Salt Substitutes. Am. Pract. & Digest Treat. 2:168, 1951.
2. Fremont, R. E., and others: Postgrad. Med. 10:216, 1951.

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(1) Burns, J. J., and others: J. Pharmacol. & Exper. Therap. *106*:375, 1952. (2) Byron, C. S., and Orenstein, H. B.: New York State J. Med. *53*:676 (Mar. 15) 1953. (3) Currie, J. P.: Lancet *2*:35 (July 5) 1952. (4) Davies, H. R.; Barter, R. W.; Goe, A., and Hirson, C.: Brit. M. J. *2*:1392 (Dec. 27) 1952. (5) Dolfel, N. E., and Griffin, A. C.: Stanford M. Bull. *2*:65, 1953. (6) Domenjoz, R.: Federation Proc. *11*:339, 1952. (7) Domenjoz, R.: Internat. Rec. Med. *165*:467, 1952. (8) Goldfain, E.: J. Oklahoma M. A. *46*:27, 1953. (9) Gutman, A. B., and Yü, T. F.: Am. J. Med. *13*:744, 1952. (10) Kuzell, W. C.: Annual Review of Medicine, Stanford, Annual Reviews, *2*:367, 1951. (11) Kuzell, W. C., and Schaffarzick, R. W.: Bull. on Rheumatic Diseases *3*:23, 1952. (12) Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952. (13) Kuzell, W. C., and Schaffarzick, R. W.: California Med. *77*:319, 1952. (14) Patterson, R. M.; Benson, J. F., and Schoenberg, P. L.: U. S. Armed Forces M. J. *4*:109, 1953. (15) Rowe, A., Jr.; Tufft, R. W.; Mechanick, P. G., and Rowe, A. H.: Am. Pract. & Digest Treat., in press. (16) Smith, C. H., and Kunz, H. G.: J. M. Soc. New Jersey *49*:306, 1952. (17) Steinbrocker, O., and others: J.A.M.A. *150*:1067 (Nov. 15) 1952. (18) Stephens, C. A. L., Jr., and others: J.A.M.A. *150*:1094 (Nov. 15) 1952. (19) Wilkinson, E. L., and Brown, H.: Am. J. M. Sc. *225*:153, 1953.

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Med. Times *81*:266 (Apr.) 1953.

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Kountz, W. B.: Ann. Int. Med. 35:1055, 1951.

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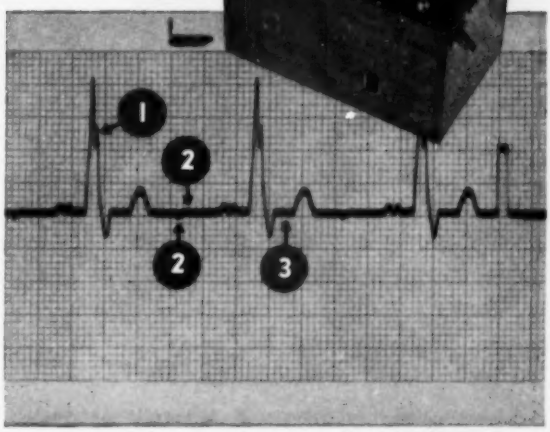

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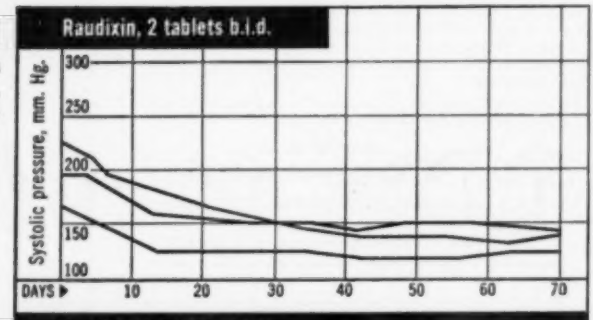

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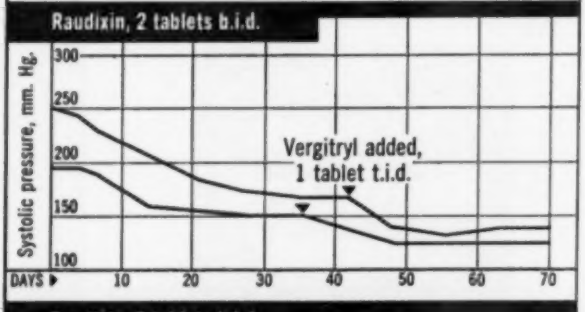
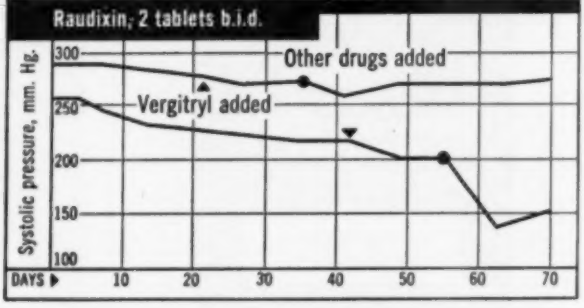
If blood pressure is not adequately controlled in four to eight weeks, Vergitryl (veratrum) may be added to Raudixin. This brings many of the remaining patients under control. Raudixin tends to delay tolerance to Veratrum, and makes smaller dosage possible.



step 3

For the few patients resistant to this combined regimen, a more potent drug may be added, for example, Bistrium (hexamethonium). The most potent drugs, which are potentially dangerous, are thus used only as a last resort in the most refractory cases.



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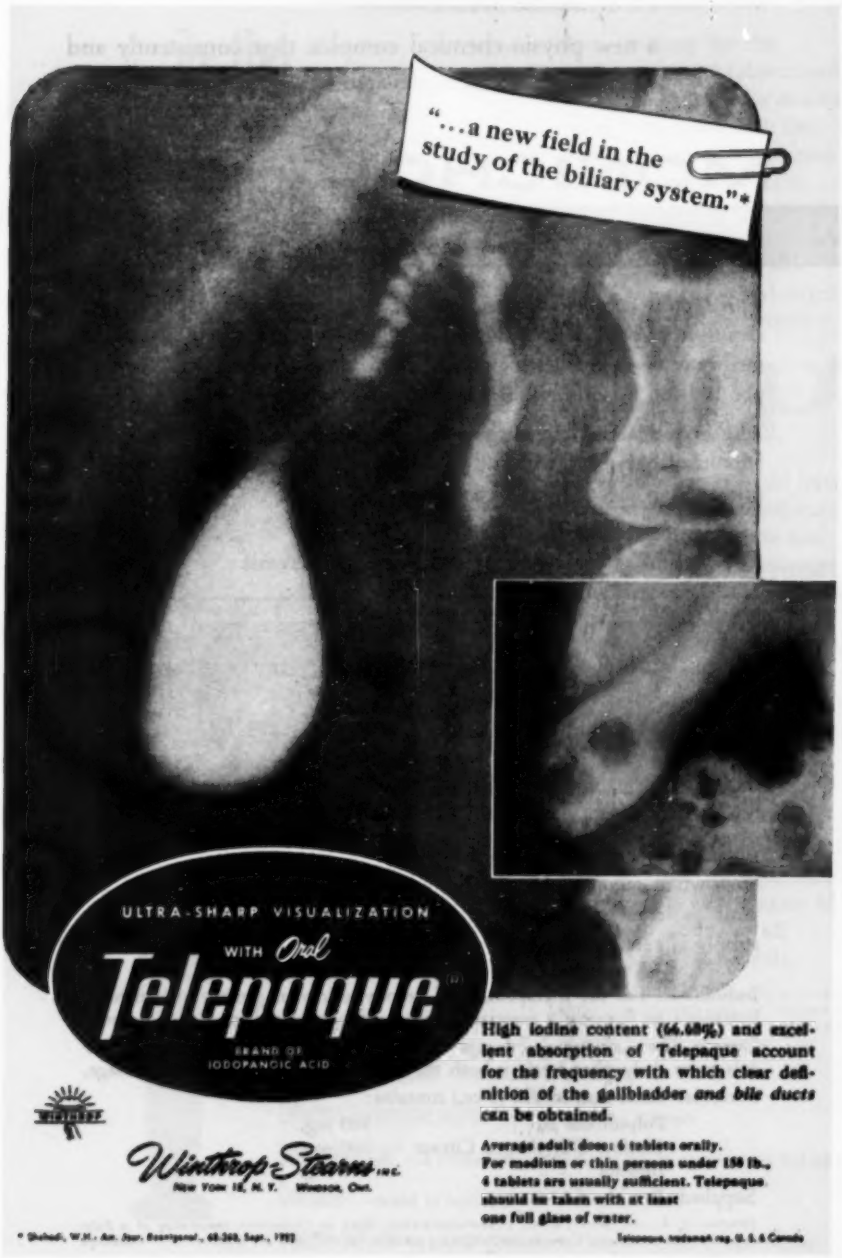
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* Shehadi, W.H.: Am. Jour. Roentgenol., 48:303, Sept., 1942
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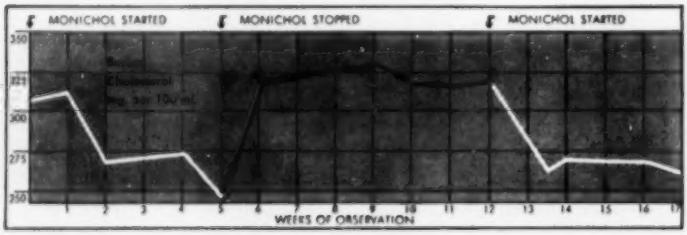

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†Sherber, D. A., and Levitas, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953. *Trademark

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1. Heck, W. E.: Reduced Ototoxicity by Combined Streptomycin-Dihydrostreptomycin Treatment of Tuberculosis, Scientific Exhibit 317, 102nd Annual Meeting A.M.A., New York, June 1-5, 1953.

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1. McHardy and Browne: Sou. M.J. 45:1139, 1952.

2. Lorber and Shay: Fed. Proc. 12:90, 1953.

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1. Riseman, J. E. F. and Brown, M. O. Arch. Int. Med. 60: 100, 1937
2. Brown, M. O. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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Phosphorus	.27 gm.	.4 gm.
Iron	1.5 mg.	4.4 mg.
Vitamin A	843 I.U.	1745 I.U.
Thiamine	.12 mg.	.7 mg.
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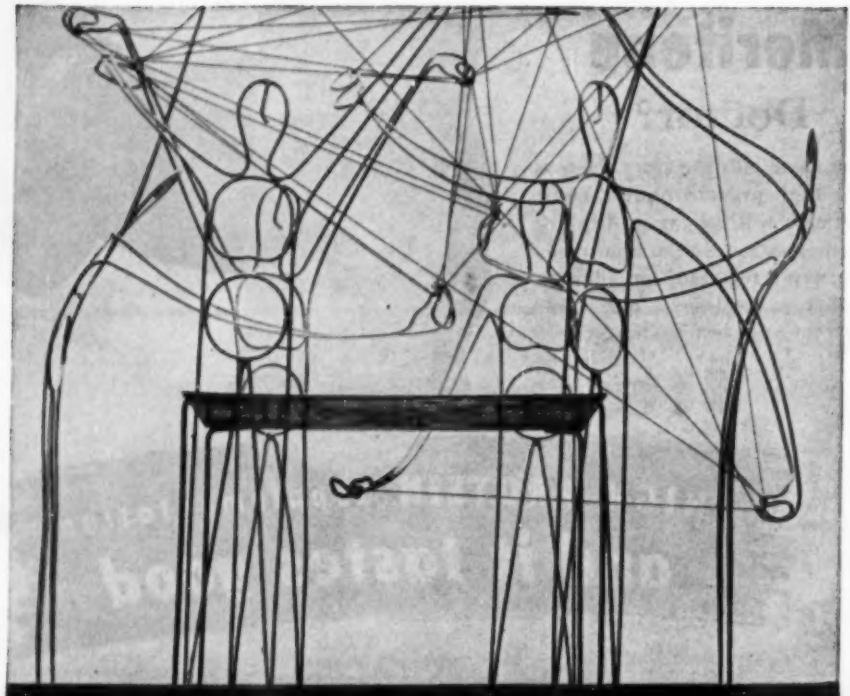

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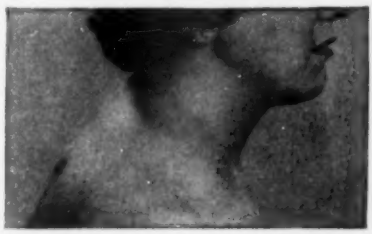
[1]Evans, R. R., and Rackemann, F. M.: *A.M.A. Arch. Int. Med.* **90**:96–127, July 1952.

Before treatment. Observe typical facies and tense sternocleidomastoid.



After therapy with CORTONE. Note relaxation of accessory muscles of respiration.

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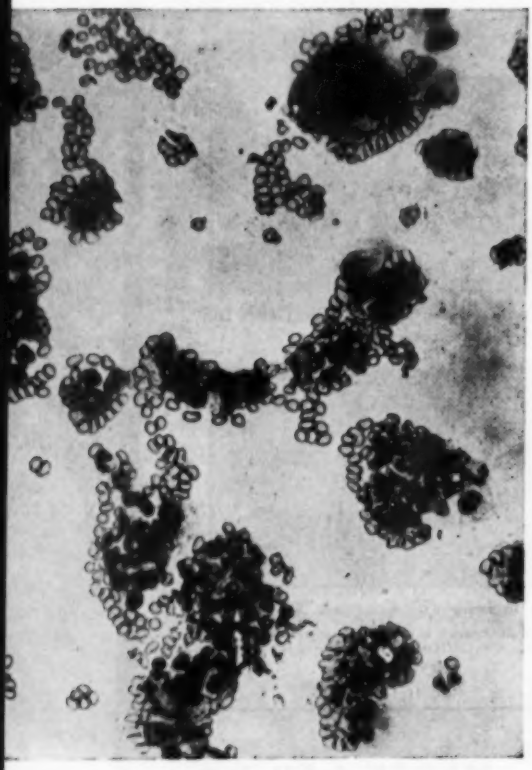
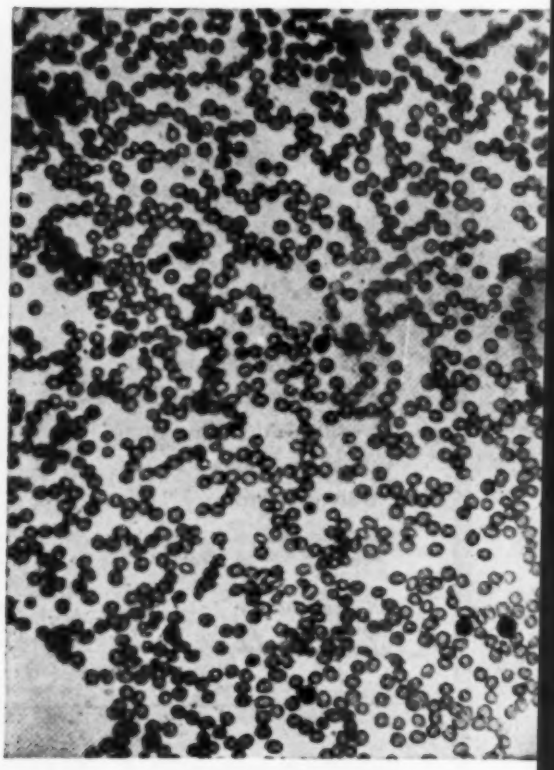


Bone marrow showing—acquired erythrocytic hypoplasia—no nucleated erythrocytes.



Same patient showing—active erythropoiesis following cobalt therapy.

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In Anemia Accompanying Infection—Roncovite

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Roncovite provides successful therapy in the great majority of *all* the microcytic and normocytic anemias commonly seen in practice. (Roncovite is of the same low order of toxicity as iron.)

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Improvement is often rapid, with the patient voluntarily reporting an increased sense of well being within a few days. Such results have been documented and repeatedly confirmed in clinical use.

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1. Case 2, Seaman, A. J., and Koler, R.; Acta Hematologica, 9:153, 1953.

2. Gardner, Frank H., J. Lab. Clin. Med.; 41:56, 1953.

3. Rohn, R. J. and Bond, Wm. H.; J. Lancet, 73:301, 1953.

PHOTOGRAPH BY PAUL RADKAI

Easy-to-administer oral antibacterial therapy

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DOSAGE: Adults, 1 or 2 tablets or teaspoonfuls q.i.d. Children, by weight and condition. Dosage schedule on request.

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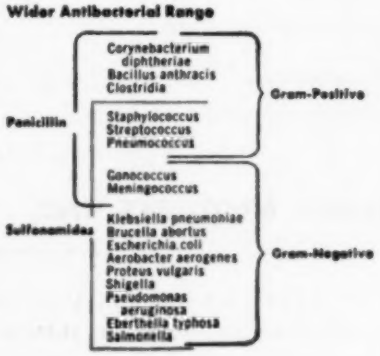

ANNALS OF
INTERNAL MEDICINE

VOLUME 39 DECEMBER, 1953 NUMBER 6

DRUG INDUCED HYPOPLASTIC ANEMIAS AND RELATED SYNDROMES *

By EDWIN E. OSGOOD, M.D., F.A.C.P., *Portland, Oregon*

THE object of this paper is to give a concise review of current concepts of the diagnosis and therapy of hypoplastic anemias and the closely related conditions known as erythrocytic hypoplasia, granulocytic hypoplasia and thrombocytic hypoplasia, and to outline briefly some of the unsolved problems relating to these disorders. A complete list of references to the literature on these subjects would be far longer than this article. The references cited have been chosen to guide the reader to readily accessible, recent articles, which in turn give references to earlier and sometimes more important papers.

CELL DIVISION AND DIFFERENTIATION

To understand the hypoplastic syndromes it is necessary to have a clear grasp of the normal processes of cell division, differentiation, release into the blood stream from the blood-forming organs, cell death and autolysis. Hypoplasia, by definition, means a cessation or decrease in the rate of cell division (a prolongation of the intermitotic interval). Figure 1 shows graphically what happens for each dividing cell. The horizontal line at the top represents one cell capable of division. The diagonal lines each represent one cell capable of differentiation. Differentiation is plotted on the ordinate. Total autolysis, rather than cell death, is represented as the base line. Time in percentage of the total life span from cell division through complete autolysis of the mature cell of the series is shown on the abscissa. It is obvious that when the blast cells divide, one of the cells must mature and the other remain an immature cell capable of division; otherwise, there would soon be no cells capable of division, or else all cells would be immature and capable of division. What determines which of the resultant cells will dif-

* From the Symposium on Anemia presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 17, 1953.

From the Division of Experimental Medicine, University of Oregon Medical School, Portland, Oregon.

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ferentiate and which will remain capable of division is as yet unknown—possibly a single cytoplasmic granule that goes to one cell and not the other, but this is pure speculation. For the erythrocytic series of cells, with a total life span of 120 days, one unit on the abscissa would equal 1.2 days, and one would have to draw a horizontal line at about the 2 per cent line on the ordinate to include all nucleated erythrocytes in the body, and at about the

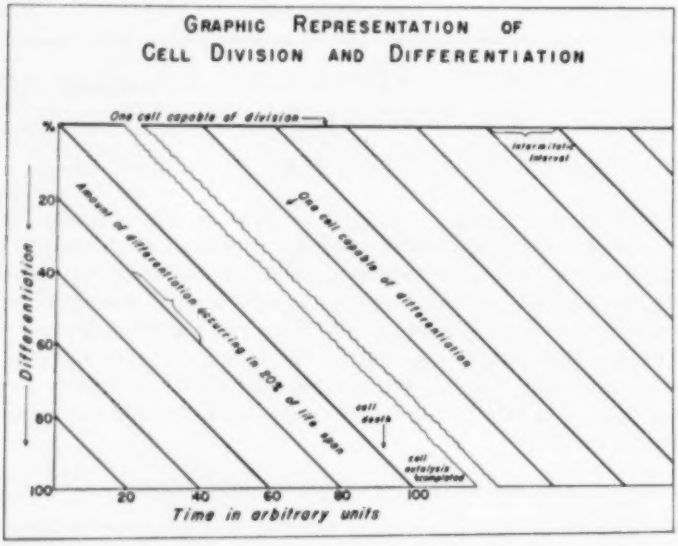

FIG. 1. The top line represents a cell capable of division; the diagonal lines, each cell derived from it capable of differentiation; the bottom line marks autolysis to that point where the cell is no longer included in erythrocyte, leukocyte or thrombocyte counts. Cell death occurs at an as yet unknown time prior to this. The graph should be thought of as extended indefinitely from each side, with the diagonal lines—here cut off—projected to the top or bottom lines respectively, and parallel diagonal lines filling these extensions. Obviously, additional parallel diagonal lines should be interpolated depending on the time scale chosen and the life span of that series from division to autolysis. As constructed, the graph would show every cell of a hypothetic series with a five day or five hour life span, if the 100 mark on the abscissa represented five days or five hours. Horizontal lines should be imagined for each series intersecting the ordinate at a point corresponding to the percentage of the total life span required to reach the end of each stage of differentiation. Differences between numbers corresponding to the points of intersection of any vertical line with any two horizontal lines would then give the total body differential count of the stages of differentiation included between those lines at equilibrium. The proportion of the total diagonal lines intersected by any vertical line between any two horizontal lines would give the total body differential count even when the intermitotic interval was changing.

4 per cent line on the ordinate to include these plus all reticulocytes. All cells above the 2 per cent line would be all nucleated erythrocytes in the marrow. All cells between this and the 4 per cent line would be reticulocytes of the blood and marrow. All cells between this and the 100 per cent line would be erythrocytes in the blood, including those that had died but not yet completely autolyzed.

For the granulocytic series, our information is not yet so accurate. The best estimates from the data available to me [1, 2]—some of it unpublished marrow culture studies—indicate that a hundred time units on the abscissa should be about 120 hours. To represent the end of each stage of differentiation, horizontal lines intersecting the ordinate should be, for the blast, pro- and early myelocyte stages, all of which are capable of division in the marrow, at the 10 per cent level; for the neutrophil myelocyte at the 15 per cent level; for the neutrophil metamyelocyte at the 30 per cent level; for the band neutrophil and release of the cells into the blood stream the horizontal line should be at the 50 per cent level, and for the segmented neutrophils, the line marking the point at death would be at about the 90 per cent level, giving a total span of the neutrophils in the blood stream of about 60 hours, and of their precursors in the marrow of a similar time period. The eosinophils (eight days) and basophils (12 days) spend a much longer time in the blood stream.[1]

For the thrombocytic series, much less accurate data are available, but the total life span, from the dividing megakaryoblast to the complete disappearance of the thrombocytes derived from it, is probably of the order of four to eight days, with about half of the time, or two to four days, in the blood stream. The fact that thrombocytes are formed by budding from mature megakaryocytes does mean that at the 50 per cent point, approximately, where the division occurs between marrow and blood, one would have to increase the number of lines, each corresponding to an individual thrombocyte, to a large number for each single line above that point. What this number is, is as yet completely unknown. It is obvious that, except in the thrombocytic series, there must be exactly one division for each cell death at equilibrium, and to represent the status of equilibrium there should be as many diagonal lines in figure 1 as there are cell deaths or cell divisions in the total time period covered by the graph.

The lines as indicated in the first part of figure 1 correspond to the percentage of cells that would be present if the time scale were five days or five hours for cells with a total life span of five days or five hours, and, of course, depending on the time scale used, one has to imagine enough lines interpolated parallel to these to correspond to the actual life span for a particular cell series. Notice that at equilibrium the percentage of each cell type in the entire body is directly proportional to the length of time the cell is in that stage of development. Of course, it must be recognized that the morphologic criteria customarily used may not correspond to the physiologic lines of demarcation. For example, not only the myeloblast but also the progranulocytes and some of the early myelocytes contain nucleoli and are capable of division.

Figure 1, as constructed, illustrates the concept of hypoplasia or cessation of cell division beginning at zero time. Note that a vertical line at any time after this will give the differential count of that cell series in the entire body.

Note that immature cells, except those capable of division, disappear from the marrow first. Only later is there any change notable in the blood. The time that hypoplasia persists is, of course, extremely variable, as indicated by the break in the chart. When cell division begins again, immature cells will first reappear in the marrow and, later, progressively more mature stages. Therefore, it is not uncommon to find a marked cytopenia in the blood, along with an increased proportion of early cells in the marrow. This has often been interpreted as maturation arrest, when it actually represents beginning cell division after a period of hypoplasia. Beginning cell division is differentiated from cell death before the differentiating cell reaches maturity, which gives a similar picture that has also been misinterpreted as maturation arrest, by the paucity of disintegrated (dead and partially autolyzed) cells in the former and abundance in the latter condition. Early cell death is probably what occurs in pernicious anemia.

Diagnosis and Differential Diagnosis

Hypoplastic anemia is actually the simultaneous presence of three conditions—erythrocytic hypoplasia, granulocytic hypoplasia and thrombocytic hypoplasia. Usually there is also some lymphocytic hypoplasia with a reduced absolute number of lymphocytes. Any one of these syndromes may occur separately or together. Since complete disappearance of cells from the blood-forming organs practically never occurs, the term *hypoplasia* was preferred to *aplasia*.[3] The most important diagnostic features of these diseases are outlined in table 1. Obviously the decrease in reticulocytes, neutrophils and thrombocytes in the blood will long precede the development of anemia because of the long life span of mature erythrocytes. To detect,

Table 1
Classification of Hypoplastic Syndromes

Severity	Hypoplastic Anemia					
	Erythrocytic Hypoplasia*		Granulocytic Hypoplasia*		Thrombocytic Hypoplasia*	
	Reticulocytes per cu. mm.	Marrow Nucleated Erythrocytes/cu. mm.	Neutrophils per cu. mm.	Marrow Granulocytic Series/cu. mm.	Clot Retraction	Marrow Thrombocytic Series/ml.†
Mild	15,000–25,000	2,000–4,000	500–1,500	4,000–8,000	Delayed or incomplete	300–500
Moderate	5,000–15,000	500–2,000	200–500	1,000–4,000	Absent 1 hr.	100–300
Severe	<5,000	<500	<200	<1,000	Absent 18 hr.	<100

* Any of these may occur alone or in any combination.
† Nucleated cells only.

reliably, a decrease in reticulocytes a method that will demonstrate all reticulocytes [4] must be used and a large number must be counted, using the Miller disk [5] or some similar method. Since there are many causes of anemia, granulocytopenia or thrombocytopenia that are not due to decreased cell division, it is obvious that a study of aspirated marrow is almost absolutely essential [6] to the establishment of a diagnosis of any one of these syndromes. The clot retraction test is much simpler and more reliable than thrombocyte counts. As done in the average clinical laboratory, thrombocyte counts are almost totally valueless. An unpublished method of Dr. Paul Aggeler appears to be the most reliable, practical method, in which blood is drawn directly from the vein into a syringe containing Rees-Ecker fixing fluid;

TABLE II

Clinical Etiologic Groups of Hypoplastic Syndromes

A.

Common, Rarely Severe, Mechanism Unknown

Groups
Bacterial infection
Viral infection
Parasitic infestation
Nutritional and endocrine deficiencies
Endogenous toxins
Congestive splenomegalies

B.

Common, May Be Severe, Will Produce Hypoplasia in Anyone

Groups	Mechanism
Ionizing radiation	Decreased cell division
Mustards	Killing of young cells
Urethanes	Mitotic poison
Antifolic compounds	Early cell death
Benzol	Unknown
Myleran[8, 9]	Unknown

C.

Rare, Usually Severe

Groups	Mechanism
Drug idiosyncrasy	Antigen-antibody reaction?
Congenital erythrocytic hypoplasia	Anomaly
Acquired erythrocytic hypoplasia	Unknown
Cyclic granulocytic hypoplasia	Unknown
Hypoplastic anemia of unknown cause	Unknown

D.

Very Rare, Usually Severe

Disease	Mechanism
Congenital hypoplastic anemia	Hereditary anomaly
Hypoplastic anemia sequel to lymphocytic leukemia	Unknown
Hypoplastic anemia sequel to myelofibrosis or osteopetrosis.	Unsuitable environment?

this is mixed and thin smears are made and stained with Wright's stain. The thrombocyte count is determined from the ratio of thrombocytes to erythrocytes seen on the smear, and an accurate simultaneous erythrocyte count.

It must be kept in mind that the descriptions given here are of the pure hypoplastic syndrome and that the patients seen will usually have mixtures of several different conditions. For example, there is often internal hemorrhage secondary to the thrombocytopenia, with associated internal blood destruction anemia or infection secondary to the granulocytopenia, with further hypoplasia or hemolysis due to the infection. Values shown in table 1 have been given in absolute numbers, since if there is loss or destruction of mature cells, the percentages might be above normal even with a normal

or decreased rate of cell production. The thick drop method [7] of megakaryocyte counting is recommended.

To see the drug-induced hypoplastic syndromes in true perspective it is necessary to have in mind the many other causes of hypoplasia listed in table 2. The hypoplasias that occur in group A rarely cause difficulty in differential diagnosis. Erythrocytic hypoplasia is the common mechanism of anemia in infection, and rather severe hypoplastic anemias may occur in kala-azar. Preponderant granulocytic hypoplasia occurs in most viral infections. Hypothyroidism and low protein intake are extremely common causes of mild hypoplastic syndromes that respond well to replacement therapy. Hypoplasias due to endogenous toxins occur commonly in uremia and hepatic toxemias. Pancytopenia associated with the congestive splenomegaly of cirrhosis and the other causes of portal hypertension is well known since it is common and should rarely be confused with the more severe hypoplasias listed in groups B and C.

In group B of table 2 the diagnosis is usually obvious from the history, and it is in this group that the mechanism of production of hypoplasias by most of these agents is relatively well understood. All of the agents listed in group B will produce hypoplasia in any person or species if the dose is large enough, so that clinical and animal studies are possible with these agents. In clinical practice, not all patients exposed to risk do develop the disease. There is a considerable range in susceptibility among different people, and when used in therapeutic doses the toxic level for each of these agents is so near the hypoplasia-producing level that some of the most susceptible individuals are likely to develop moderate or severe hypoplasias while others escape. The full therapeutic effects of these agents are difficult to elicit without a dosage that approaches the hypoplasia-producing range.

Group C of table 2 includes the drug idiosyncrasy hypoplasias, to be considered in more detail later, and also several rare diseases. Some cases of congenital erythrocytic hypoplasia respond to cortisone or ACTH therapy,[10] and some cases of acquired erythrocytic hypoplasia respond to cobaltous chloride,[11] 50 to 100 mg. three times daily after meals, continued for three to four months. The cause of cyclic or periodic granulocytic hypoplasia [12] is as yet completely unknown. Hypoplastic anemia of unknown cause is the term used when the most careful history fails to reveal a cause. Food idiosyncrasy may be a factor in some of these cases. Undiagnosed hypoplasia of other etiologies, which a more careful history, physical or laboratory study would have diagnosed, will also be placed in this category. All classes of severe hypoplastic anemia are rare, only 600 cases from all causes being reported for the registration area of the United States in 1949.

The conditions listed in group D of table 2 are extremely rare, but usually readily diagnosed. Congenital hypoplastic anemia (Fanconi's syndrome [13]) is associated with many other anomalies.

The hypoplasias due to drug idiosyncrasy, with which this paper is

chiefly concerned, differ from those listed in group B of table 2 in that the administration of the responsible agent, even in large doses, will produce hypoplasia in only a very small percentage of the population exposed to risk. These agents usually do not produce hypoplasia in any dose in other species, so that, as yet, it has been impossible to study in animals the mechanism of the hypoplasias produced by these agents. The only practical source of investigative material is a person who has recovered from a hypoplasia due to one of these drugs, and such a person is suitable for study only with the same drug or a closely related drug. Furthermore, a repeated administration of the same drug to such a patient is an extremely hazardous procedure. Therefore, the most promising line of such an investigation would appear

TABLE III

Agents Known to Produce Hypoplastic Syndromes of Drug Idiosyncrasy Type

A.

Hypoplastic Anemia

High Risk	Low Risk
Arsenobenzols[14]	Phenylhydantoins[15]
Chloramphenicol[13]	Sulfonamides[19]
Mesantoin[16]	Trimethadione[20]
Gold preparations[17]	Quinacrine[21]

B.

Chiefly Granulocytopenia

High Risk	Low Risk
Aminopyrine[22]	Antihistaminics[26]
Nitrophenols[23]	Phenothiazines[27]
Thiouracils[24]	Procaine amide hydrochloride[28]
Thiosemicarbazones[25]	

C.

Miscellaneous Group

Phenylbutazone[29]	Presidon*[34]
Sedormid†[30]	Methoin*[35]
Phenurone*[31]	Quinidine†[36]
Methimazole*[32]	Streptomycin[37]
Amithiozone*[33]	Mercurial diuretics*[38]

* Granulocytopenia only.
† Thrombocytopenia only.

to be marrow culture studies with the recovered patient's marrow or with normal marrow and the recovered patient's serum.

All of these hypoplasias have in common the fact that there is usually a time lag between first exposure to the drug and the onset of the symptoms. Repeated or prolonged exposures may lead to a higher incidence than first exposures, but the severity of the hypoplasia is relatively unrelated to the dose, and very small doses may bring on very severe hypoplasias when idiosyncrasy has occurred. There appears to be a higher incidence of an allergic history in individuals who have developed such hypoplasias than in the general population. Putting these facts together, the most plausible mechanism of the production of the drug idiosyncrasy group of hypoplasias, at least to this author, is that the drug or a metabolite behaves as a hapten and com-

bines with some specific protein in the cell to form a new protein that is antigenic; the patient then develops immune antibodies that react with the specific protein in such a way as to kill the cell, or prevent its division or deprive it of an essential enzyme system or nutrient. This mechanism probably accounts for nearly all drug idiosyncrasies and for the collagen group of diseases. The mechanism of developing circulating autoagglutinins in acquired hemolytic anemias is probably similar, but as yet there is no conclusive proof for this theory.

The drugs reported to have produced hypoplastic syndromes are listed in table 3. Many of these drugs have numerous different proprietary names, some of them more familiar than the official name. Furthermore, many of these drugs are incorporated into proprietary mixtures under other trade names, so that the drug history in any patient with a hypoplastic syndrome should include the reading of the fine print on the original bottle of any medication that has been taken within the preceding two or three months, which may necessitate a visit to the pharmacy where the medication was obtained.

The columns headed *high risk* and *low risk* are only relative estimates by the author. Actually, the incidence of hypoplasias is comparatively low for all the drugs listed. Only for quinacrine [21] (Atabrine) are really reliable data available. Here the incidence is approximately one in 25,000 persons exposed to risk per year. The order in which the drugs are listed is the author's estimate of the relative risk in terms of the percentage of total persons receiving the drug who are likely to develop a hypoplastic syndrome. Because of the lack of data, these estimates are only roughly approximate. Aminopyrine probably gives the highest incidence of any, which may be as high as one in 500 persons exposed to risk. It is vitally important that more data be accumulated on the relative risks of these agents. In order that this may be possible, it has been requested that all persons seeing cases of any of these drug-idiosyncrasy hypoplastic syndromes report the cases in full to the Council on Pharmacy and Chemistry of the American Medical Association.

Part A in table 3 includes all the groups of drugs that have been well established as producing drug idiosyncrasy hypoplastic anemia. Some of them produce one or more of the related syndromes more often than a true hypoplastic anemia.

Part B includes the drugs in which, to date, granulocytic hypoplasia alone has been reported. Most of the antihistaminics so far reported as producing agranulocytosis belong to the ethylene diamine or phenothiazine groups. The thiosemicarbazones include a large number of agents proposed for the treatment of tuberculosis. It is as yet not certain that the mechanism for all of these is actually granulocytic hypoplasia. For aminopyrine, at least, Moeschlin [39] has evidence that this may be a circulating autoagglutinin for leukocytes analogous to that for the erythrocytes and thrombocytes in

some cases of acquired hemolytic anemia,[40] and to the circulating thrombocyte agglutinin in some cases of thrombocytopenic purpura.[41, 42]

Part C includes Sedormid [39] and quinidine,[36] which produce only thrombocytopenia, probably not by the method of thrombocytic hypoplasia, but by a circulating agglutinin. It also includes drugs [29, 31-35] so recently studied that the mechanism of action is still uncertain, and those where the incidence

TABLE IV

Differential Diagnosis

A. Hypoplastic Anemia or Erythrocytic Hypoplasia Due to Drug Idiosyncrasy	
All other hypoplastic anemias.	Other etiology demonstrable. None of listed drugs taken, or wrong time relationship.
Aleukemic and subleukemic leukemias.	Splenomegaly, marrow findings.
Other myelophthisic anemias.	Evidence of neoplasm, bone pain, marrow findings.
Internal erythrocytic destruction anemias.	Reticulocytosis, icterus, autoagglutination.
B. Granulocytic Hypoplasia Due to Drug Idiosyncrasy	
Early aleukemic or subleukemic leukemias.	Marrow findings; buffy-coat blood smear.
All other granulocytic hypoplasias.	History.
Simple leukopenias.	Granulocytes > 1,500 per cu. mm.
C. Thrombocytic Hypoplasia Due to Drug Idiosyncrasy	
All other thrombocytic hypoplasias.	History.
Thrombocytopenic purpura, unknown cause.	Increased megakaryocytes in marrow.
Allergic thrombocytopenic purpura.	Allergic and drug history; eosinophilia.
Allergic capillary purpura.	Arthralgia and/or partial intestinal obstruction syndrome. Normal clot retraction.
Lupus erythematosus disseminatus.	L. E. cells > 10 per 500 granulocytes.
Thrombotic thrombocytopenia.	Hemolytic anemia picture.
Acute monocytic leukemia.	Gum hyperplasia. Peroxidase stain of buffy coat smears. Auer bodies. Supravital studies of blood and marrow.
Hereditary thrombocytopenic or thrombocytopathic purpuras.	Long, familial history.
Hypoprothrombinemias.	Jaundice, liver disease and prothrombin < 10%.
Scurvy.	Dietary history. Rare. Bleeding into gums; low leukocyte ascorbic acid.

is known to be very low, as is true of streptomycin [37] and the mercurial diuretics.[38]

Since table 3 is incomplete, often listing only group names, and since new, potentially hazardous drugs are constantly being introduced, it is worthy of note that the majority of agents so far reported to cause these symptoms fall in the pharmacologic groups of anticonvulsants, antihistaminics, antimicrobial agents, antithyroid agents, heavy metals, sedatives and spasmolytics. It is also noteworthy that most of these agents have a five- or six-membered ring structure with a nitrogen radical in the ring or close to it.

Therefore, it is probably wise to use any new drug with these pharmacologic or chemical properties as though it had been proved to carry some risk of producing hypoplasia.

Table 4 lists the chief points in the differential diagnosis of the drug idiosyncrasy group of hypoplastic syndromes from the other conditions with which they may be confused. So far the most frequent error is mistaking acute or subacute leukemias for hypoplastic anemia. These give a pancytopenia and a clinical picture indistinguishable from that of hypoplastic anemia, except for the presence of enlarged spleen and lymph nodes, although many cases have no enlargement of the spleen and lymph nodes, at least in their early stages. The presence of enlargement of spleen or lymph nodes excludes the drug idiosyncrasy group of hypoplastic syndromes. Only marrow examination will establish this differential diagnosis with certainty. Examination of thin smears of the leukocyte buffy coat of the blood will often yield diagnostic cells in the leukemias. Since marrow is sometimes difficult to aspirate because the cells adhere to each other so firmly in aleukemic or subleukemic leukemias, a low cell count in the aspirated marrow is not enough to make the differentiation. The most reliable criteria for differentiating the leukemias from the hypoplastic syndromes are, in the author's experience, the facts that the involved cell of the leukemias nearly always shows a larger total amount of nucleolar material than the corresponding normal cell, and that there is nearly always a higher percentage of disintegrated cells, indicating early cell death in the leukemias. In some instances repeated marrow aspirations may be necessary before a final differential diagnosis is possible. Congestive splenomegalies [43] with pancytopenia or granulocytopenia are easily differentiated by the findings of hyperplastic marrow and the enlarged spleen.

TABLE V

Prophylactic Therapy

Never give listed drug when risk of drug appears greater than risk of disease. Check w.b.c., Hb., reticulocyte count and clot retraction before starting, at intervals, and after stopping. Warn patient to report *immediately* sore gums or throat, petechiae, ecchymoses or bleeding gums. See that involved drug or related compound is never again given to patient who recovers.

PREVENTION AND TREATMENT

When a hypoplastic syndrome occurs, the mortality rate is high and therapy is expensive and may be prolonged. Therefore, it is of the utmost importance for every physician to know the methods of preventing the occurrence of as many as possible of these cases, as outlined in table 5, and ways of reducing the severity of those cases that do occur. A review of the reported cases of hypoplastic anemia following the administration of chloramphenicol should emphasize to anyone the extreme importance of weighing

the risk of the disease against the risk of the drug. Most of the fatal cases occurred in persons treated for minor illnesses, for which safer therapy was available. Many of the patients alive at the time the chloramphenicol survey [15] was made have subsequently died, some of these more than seven months after the last dose of the drug was administered. Few had hematologic studies at any time prior to onset of symptoms four to eight weeks after the drug had been discontinued.

It is impossible to overemphasize the importance of writing on the front of office and hospital charts and on a card to be carried by the patient at all times, in large type: **"John Doe has an idiosyncrasy to (name of drug or compound) that led to the development of (name of hypoplasia). Under no circumstances should he ever again receive this compound or any closely related compounds."** The patient should be given explicit instructions to show or read this card to any physician he may have occasion to consult in the future.

TABLE VI

Therapy* of Hypoplastic Syndromes Due to Drug Idiosyncrasy

	STOP THE DRUG!
Thrombocytic hypoplasias	Blood transfusions < 6 hrs. old as often as necessary to keep some clot retraction at 1 hr.
Granulocytic hypoplasias	Procaine penicillin 300,000 U and streptomycin 0.5 gm. I.M., b.i.d. with added penicillin G 500,000 U doubled q 48 hours if fever not controlled.
Erythrocytic hypoplasias	Blood transfusion whenever Hb. drops below 8 gm.

* Cortisone or ACTH in full doses with usual precautions and/or cobaltous chloride 50 to 100 mg. t.i.d., p.c. probably worth trying.

When a diagnosis is established, immediately stop the administration of any drug that might possibly have been a factor in the production of the hypoplasia, with the possible exception of streptomycin in patients whose lives depend on its use. Use the other therapeutic measures outlined in table 6 according to the results of daily observations of the patient and daily laboratory checks of the total neutrophils and clot retraction time, using the other tests listed in table 1 at frequent intervals. Transfusions of fresh blood may have to be given every six hours initially for two to four transfusions to control thrombocytopenic bleeding, and may have to be given daily to keep it under control. If erythrocytosis or hypervolemia threatens from this regimen, the patient may be bled an equivalent amount just before each transfusion without significant loss of thrombocytes, because of their short life span. The use of polycythemic blood,[44] siliconed equipment [45] and methods of concentrating thrombocytes [46] is desirable when available, but is still impractical outside of the largest medical centers. Calcium, vitamins K and P preparations, and the various substances that have been proposed as stimulators of cell growth and differentiation are valueless in the treatment

of these syndromes. There are no known substitutes for fresh blood transfusions and antibiotics. The hazards of the development of thrombocyte agglutinins, outlined by Sprague et al.,[45] are undoubtedly real, but as yet there is no alternative to multiple transfusions, with all their hazards,[47] when death from thrombocytopenic bleeding or erythrocytic hypoplasia threatens.

The earlier the disease is recognized, the sooner the drug is stopped, the milder the hypoplasia, and the sooner clot retraction, neutrophils and reticulocytes begin a steady increase, the better the prognosis; however, patients have been known to recover even after several years of hypoplasia. Thrombocytic hypoplasia carries the greatest risk, granulocytic hypoplasia the next, and erythrocytic hypoplasia the least, but accurate statistics on prognosis are still unavailable.

Suggested Studies

As yet unknown are the following: The statistical risk for each drug; whether the drug or a metabolite produces the syndrome; what is the exact chemical compound acted on; what regulates normal cell division and differentiation; whether a specific agglutinin for immature cells develops; what, if any, is the rôle of complement; what is the exact survival time of these cells in vivo and in vitro, and how can they be better preserved and separated either for in vitro studies or for therapeutic administration; and whether it may be possible to grow in vitro cells in sufficient quantities for therapeutic use.

Statistical data from the entire country are being accumulated by the Council on Pharmacy and Chemistry of the American Medical Association, but the success of this project depends on the receipt of reports from all physicians of all cases encountered. The instigation of supplementary studies in metropolitan hospitals is imperative. For most studies, marrow and blood of patients known to have recovered from a hypoplasia known to have been due to a particular drug are essential. Therefore, such studies should be undertaken by persons in large metropolitan centers where such patients may be available in sufficient numbers. The metabolic patterns of these patients, as compared to negative controls, should be studied by the method of Roger Williams.[48] The marrow culture technic[49] would permit studies of the chemical and enzyme composition and turnover rates[50] of normal and involved cells, and of the effects of drugs and metabolites on the recovered patient's marrow, or on a normal marrow grown in a medium containing the recovered patient's serum. It would also permit studies of the normal regulators of cell division (absence of the mature cell?) and differentiation, and the effects of humoral growth stimulators.[51, 52]

Chemists and pharmacologists should continue their efforts to develop therapeutic compounds that have the desired beneficial actions without the hazard of producing hypoplasia. They should also continue efforts to determine the chemical groups that are responsible for the hazards so that

drugs with these structures can be avoided. The design of initial human trials of new drugs should be planned in consultation with a competent statistician and the results analyzed by the statistician before general release of the drug, although, because of the low incidence of these complications, it will probably be impossible to exclude risk of these diseases in any series of practical size.

Everything we do in life, from taking a bath to crossing a street, carries some risk, so that the most we can hope to do is carefully weigh the risk against the benefits to be derived. Hypoplasias will always be with us.

Summary

What is known of the mechanism, diagnosis and treatment of the hemic hypoplastic syndromes has been outlined, and specific diagnostic, prophylactic and therapeutic criteria and regimens are offered. Much remains to be learned, and suggestions for further studies are presented. At the present time, concentrated efforts on the part of every practicing physician toward prevention of the occurrence of the more severe cases of these syndromes offer most promise of reducing mortality and morbidity.

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CLINICAL EVALUATION OF GITALIN IN THE TREATMENT OF CONGESTIVE HEART FAILURE *

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The cardiac glycoside, gitalin, was first isolated from *Digitalis purpurea* by Kraft 40 years ago.[1] It has been used extensively in Europe, where some investigators believed it to be superior to other digitalis glycosides.[2, 3] Studies reported from American clinics during 1934–1938 expressed only limited enthusiasm for its merits,[4, 5, 6] and it was not accepted as standard therapy.

Interest in the drug has recently been re-awakened by the introduction of an amorphous form of gitalin which was stable and uniform,[7] and which was found to equal other glycosides in its ability to induce adequate initial and maintenance digitalization.[8] In addition, it was one third less toxic than digitalis leaf, digitoxin or Digoxin.[9, 10] The present study was undertaken to observe further the clinical application of this drug in the treatment of congestive heart failure.

Method of Study

The drug used was amorphous gitalin, each scored tablet containing 0.5 mg. of the glycoside.†

Because this is a new drug, its characteristics have been summarized in table 1. Details elaborating its clinicopharmacologic action will follow in the course of this report.

Sixty-eight patients were studied. The majority were seen in the adult cardiac clinics and medical wards of the Los Angeles County Hospital; a small number were private patients.

The patients were treated for from one to 12 months; the average duration was five and one-half months. Once digitalized, patients were observed first at semi-weekly or weekly intervals and later at semi-monthly or monthly periods. Ages of the patients varied from 20 to 90 years, the average age being 56.3 years. More than 70 per cent were between 50 and 70 years, which is the age group comprising the majority of patients admitted to this hospital. There were 35 males and 33 females. Fifty-eight were Caucasians, eight were Negroes and two were Orientals.

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† Gitalin was supplied by White Laboratories, Inc. It is commercially available under the trade name of Gitaligin.

Table 2 shows the etiologic, anatomic and physiologic diagnosis of patients studied. The three most common causes of heart disease—hypertension, arteriosclerosis and rheumatic fever—were about equally represented. There were eight cases of syphilitic heart disease and one of cor pulmonale. The wide variety of anatomic changes due to myocardial enlargement and valvular lesions is obvious in table 2. Twenty-five patients had auricular fibrillation and only slightly more than half had regular sinus rhythm. Functional classification based on American Heart Association criteria showed six in Class II, 52 in Class III and 10 in Class IV.

The patients were divided into three groups. Group I comprised those who were completely digitalized with gitalin. They had received either no

TABLE I

Clinicopharmacologic Properties of Gitalin

Derivation	*Digitalis purpurea.*
Appearance	Amorphous white powder.
Uniformity	Constant from batch to batch.
Absorption	Rapid and complete from gastrointestinal tract.
Route of administration	Oral.
Dissipation	Rate of excretion between the rapidly excreted Digoxin and slowly excreted leaf or digitoxin.
Range of toxicity	Less toxic than other glycosides. Digitalizing dose is about ⅓ amount of the toxic dose.
Dosage by rapid method	2.5 mg. first, then 1.0 mg. every 6 hours, or 1.0 mg. every 4–6 hours until toxic or therapeutic effect appears (usually 24–48 hours).
Dosage by slow method	A single dose of 1.5 mg. daily, or 1.5 mg. t.i.d. until toxic or therapeutic effect appears (usually 4–7 days).
Symptoms of toxicity	Same as for other glycosides, i.e., anorexia, nausea, vomiting, color-vision, ectopic beats, ST-T changes.

previous digitalis whatsoever, or none during the preceding month. Group II consisted of those who were already digitalized with and maintained on digitalis leaf, digitoxin or Digoxin. Gitalin was substituted for the maintenance drug and the clinical effect noted. Group III consisted of patients in severe congestive heart failure in whom the other glycosides caused toxicity, since the effective therapeutic dose often approximated the toxic dose. These were the problem cases of digitalis maintenance. Because of the wider margin between its therapeutic and its toxic dose, gitalin has been shown to be effective when no other glycoside could control failure due to toxicity. This characteristic has been claimed as its unique advantage over the other glycosides.[10, 11, 12]

Results

The criteria for adequate digitalization used in this study consisted of clinical improvement such as loss of edema, râles and hepatomegaly, or decrease in heart rate to optimum in patients with auricular fibrillation. An attempt was made in some instances to reach mild toxicity and then to reduce the dose slightly to remain below the toxic level. However, in every case the clinical improvement was so remarkable prior to any noted toxicity that it was felt there was no indication to reach toxicity. There were therefore no deliberate or inadvertent instances of toxicity in these patients.

Group I: Fifteen patients were digitalized with gitalin. Most had never received any form of digitalis previously. In the case of the small number

Table II

Type of Heart Disease Among 68 Patients Treated with Gitalin
(Classified According to American Heart Association Criteria)

Etiology		Anatomic Findings		Physiologic Findings (besides failure)	
Disease	No. of Patients		No. of Patients		No. of Patients
		Left ventricular enlargement—			
Rheumatic fever	23	a. Slight	15	Sinus rhythm	36
Hypertension	12	b. Moderate	27	Auricular fibrillation	25
Arteriosclerosis	11	c. Marked	12	Ectopic beats	3
Hypertension and arteriosclerosis	9	Right ventricular enlargement	7	Paroxysmal auricular tachycardia	1
Syphilis	8	Normal heart size	7	Bigeminy	1
Hypertension and rheumatic fever	3	Valve lesions—		Complete heart block	1
Hypertension and syphilis	1	a. Mitral stenosis	24	Auricular flutter	1
Cor pulmonale		b. Mitral insufficiency	23		
		c. Aortic stenosis	14		
		d. Aortic insufficiency	19		
		e. Tricuspid insufficiency	4		
		f. Pulmonary insufficiency	1		

who had, a time interval of one month or more had elapsed since the last dose had been given. Table 3 shows the amount of gitalin given to achieve digitalization. As has been customary with other glycosides, its administration was termed "rapid" if the desired digitalis effects occurred within 24 to 48 hours. The method was considered "slow" if more than 48 hours were required for digitalization. The effective digitalizing dose was studied by the two methods.

Table 3 shows the total doses in each of four patients who were treated rapidly. The dose was 1.0 mg. three, four or six times per day until digitalization was attained. One patient required 1.5 mg. every four hours for four doses. The digitalizing dose varied from 4.5 to 8.0 mg.; the average was 6.5 mg.

TABLE III

Gitalin Dosage Required for Initial Digitalization

Daily Dose	No. Patients
Rapid Method	
1.0 mg. t.i.d. for 24 hours	1
0.5 mg. t.i.d. for 24 hours 1.5 mg. q 4 hr. for 4 doses	1
1.0 mg. q 4 hr. for 8 doses	1
1.0 mg. q 6 hr. for 8 doses	1
Slow Method	
0.5 mg. t.i.d. for 4 days	2
0.5 mg. t.i.d. for 4 days 0.5 mg. b.i.d. for 3 days	2
0.5 mg. t.i.d. for 6 days	1
0.5 mg. t.i.d. for 7 days	4
0.5 mg. q.i.d. for 5 days	1
0.5 mg. q.i.d. for 7 days	1

The slow method required three to seven days in the group studied. The digitalizing dose varied from 5.0 to 8.5 mg., with an average of 7.0 mg. This was slightly higher than the rapid method. (One patient was an exception, requiring 11.5 mg.) Computation of the digitalizing dose is empiric because exact studies on dissipation of the drug remain to be published.[5] Hejtmancik and Herrmann have suggested that, in computing the digitalizing dose by the slow method, after the first 48 hours 0.5 mg. of the drug be considered excreted and be subtracted from each daily increment necessary thereafter for digitalization.[11] This rule was followed in computing the effective digitalizing dose in this group of patients.

The procedure followed in the slow method was to give one tablet three times a day or four times a day as long as necessary until clinical improve-

TABLE IV

Replacement of Maintenance Digitalization by Gitalin in 45 Patients

Drug Replaced	Maintenance Dose of Drug Replaced	Number of Patients	Gitalin Dose Adequate for Replacement
Digitalis	0.1 gm. daily	28	0.5 mg. daily
	0.1 gm. daily	1	0.25 mg. daily
	0.1 gm. daily	1	0–5 mg. daily+2 extra dose/wk.
Digitoxin	0.1 mg. daily	7	0.5 mg. daily
	0.2 mg. daily	1	Alternate 0.5–1.0 mg. daily dose
	0.2 mg. daily	1	0.5 mg. daily
Digoxin	0.25 mg. daily	2	0.5 mg. daily
	0.25 mg. b.i.d.	1	0.5 mg. daily
	0.25 mg. b.i.d.	1	1.0 mg. daily
	0.25 mg. t.i.d.	1	0.25 mg. daily+2 extra dose/wk.
	0.25 mg. b.i.d.	1	0.25 mg. daily+2 extra dose/wk.

ment was detected or toxicity was reached. Usually four to seven days were required for the appearance of therapeutic effect, and patients were then changed to maintenance doses.

Group II: Forty-five patients previously digitalized and satisfactorily maintained with other glycosides were transferred to maintenance doses of gitalin. Table 4 shows the number of patients transferred to this therapy and the dose of gitalin necessary to continue desirable control of congestive failure. Twenty-eight of 30 patients previously on whole leaf were maintained on 0.5 mg. of gitalin daily. Seven patients who had been on 0.1 mg. of digitoxin daily responded favorably to 0.5 mg. of gitalin daily. Three of the six patients previously administered Digoxin were effectively changed to 0.5 mg. of gitalin daily. The other three patients required slightly larger amounts. Thus 85 per cent of the patients in this group were changed to 0.5 mg. gitalin daily with satisfactory maintenance of therapy and without toxic effects.

Group III: This group consisted of eight patients in whom digitalis leaf, digitoxin or Digoxin could not be given in effective amounts because of toxicity. Gitalin was substituted for the offending drug, with subsequent improvement in cardiac status, disappearance and continued absence of toxicity, and easier management of congestive failure. Although diuretics, low sodium diet, bed-rest and other adjuvant therapy were used in each patient, the following histories will stress some of the shortcomings of digitalis therapy, and emphasize how gitalin was used in the management of these problem cases.

Case Reports

Case 1. This patient was a 54 year old white male newspaper reporter with hypertensive arteriosclerotic heart disease who had been in failure for six years. He had sinus rhythm and marked enlargement of the left ventricle, and was in function and therapeutic Class IV-E. For nine months, while on digitalis leaf, 0.1 gm. daily, he became increasingly orthopneic and had increasingly frequent attacks of angina. Dosage was then increased to alternating amounts of 0.1 gm. and 0.2 gm. per day. Dyspnea improved temporarily, but he developed toxic symptoms of nausea and vomiting. He voluntarily discontinued digitalis to relieve the gastrointestinal symptoms, but this step led to frequent bouts of acute pulmonary edema. While he was hospitalized it was observed that the vomiting would disappear after digitalis was discontinued for four days, but would return consistently with renewed use of the drug. Attempts at therapy with smaller doses were unsuccessful. He remained impaled on this dilemma for nine months. He was one of the first patients to be given gitalin, in doses of only 0.5 mg. daily. This amount sufficed to control his heart failure comfortably for the succeeding eight months. There was no gitalin toxicity during this time.

Comment: This patient represented difficulties in digitalis maintenance due to digitalis leaf toxicity. The progression of heart disease had reached such a degree that the amount of digitalis necessary to increase cardiac efficiency was perilously close to the amount which caused toxic symptoms.

Hence, even the attempt to balance the maintenance dose delicately was of no avail.

This case further demonstrates how drug intolerance leading to voluntary discontinuation of digitalis by patients may be a real problem, since, in its wake, further increase in cardiac decompensation is the rule. Case 3 also demonstrates this therapeutic problem.

Case 2. This patient was a 57 year old white housewife with arteriosclerotic-hypertensive heart disease who had been in failure for 24 months. She had Grade I cardiac enlargement, angina and sinus rhythm, and was in Class III-D. She had been started on digitoxin 14 months previously and was taking 0.1 mg. daily. During this time she was seen in the clinic at approximately monthly intervals because of anorexia, nausea and vomiting due to digitoxin toxicity. All symptoms promptly disappeared when the drug was temporarily discontinued. A therapeutic level of digitoxin without toxic side reactions was difficult to attain. She was then given gitalin, 0.5 mg. daily, and during the succeeding three months congestive failure was controlled without toxic symptoms.

Comment: This patient illustrates, as did case 1, how maintenance doses of gitalin were easily tolerated, whereas those of the leaf or of digitoxin caused severe toxicity.

Case 3. This patient was a 72 year old white housewife who had hypertensive heart disease, Grade IV cardiac enlargement and sinus rhythm, and was in Class IV-D. She had been in failure for four years. Maintenance therapy was difficult due to frequent bouts of anorexia, nausea and vomiting. She had stopped taking digitalis three months prior to hospitalization because it "made her too sick." She was admitted in marked congestive failure. Digitalization was again attempted, but after 1.0 mg. of Digoxin was given nausea and vomiting appeared and the drug was discontinued. The following day gitalin was started. She was given 0.5 mg. twice daily for three days and then 0.5 mg. once daily thereafter. The response was satisfactory. Her congestive failure markedly improved, and she became ambulatory and was maintained on a dose of 0.5 mg. daily.

Comment: Cases 1, 2 and 3 represent correction of the toxic state in congestive failure treated by the three common glycosides used today: digitalis leaf, digitoxin and Digoxin. In case 3 the required dose of gitalin was more than in the other two patients. This further illustrates the established concept that holds in gitalin therapy as well as in the other glycosides: that the ultimate effective maintenance dose of a digitalis preparation is an individual experiment in each patient.

Case 4. This patient was a 61 year old Caucasian male with syphilitic heart disease, cardiac enlargement Grade II, sinus rhythm, right bundle branch block and aortic insufficiency. He was evaluated to be in Class III-C. He had been in failure for the preceding 12 months, and during the last 11 months had been taking 0.1 gm. of digitalis daily. He was admitted to the hospital because of nausea, vomiting and disturbance in color-vision. All digitalis was discontinued for 30 days. He was later re-digitalized with digitoxin and was discharged from the hospital on a maintenance dose of digitalis leaf, 0.1 gm. daily. After four days, he was re-admitted because of the return of nausea, vomiting and disturbed color-vision, and the onset of bigeminy. The digitalis was discontinued for five days, and the toxic symptoms

abated and the bigeminal rhythm disappeared. He was then given gitalin maintenance of 0.5 mg. per day. He had no toxic signs or symptoms and his failure was well controlled. He maintained this improved state for 30 days, following which he had a gastrointestinal hemorrhage and died.

Comment: This patient demonstrated a more severe type of digitalis poisoning than the previous ones, in that bigeminal rhythm appeared. It was considered prudent, therefore, not to start gitalin therapy until the dysrhythmia had disappeared. It is of interest and importance that the average maintenance dose of gitalin of 0.5 mg. once daily sufficed to achieve control without toxicity for one month prior to death from noncardiac causes.

Case 5. This patient was a 77 year old Caucasian female with hypertensive heart disease, cardiac enlargement Grade I and auricular fibrillation, and was in Class IV-D. She had been in failure for nine months. She had been on maintenance digitalis leaf therapy of 0.1 gm. daily for three months prior to admission to the hospital. On entry she was in extreme failure, with frequent ventricular premature beats; because of toxicity, digitalis was discontinued. She showed slight improvement on low sodium diet and mercurials, and was later discharged without digitalis. She was re-hospitalized one month later. She was digitalized with gitalin, 1.0 mg. three times daily for one day, 0.5 mg. three times daily for one day, then 0.5 mg. daily. Her heart rate dropped from 104 to 70 beats per minute and remained at this level. There was no toxicity on this program and her congestive failure improved.

Comment: This patient's congestive failure increased while she was on a maintenance dose of digitalis leaf of 0.1 gm. daily. At the same time she exhibited evidence of extreme digitalis intoxication, which may have initiated the retrogressive clinical course and further interfered with cardiac function. The caution observed in case 4, of withholding all digitalis preparations until myocardial irritation had abated, was also followed here. When digitalization was later accomplished, it was of interest that the final effective dose of gitalin was only 4.5 mg., and maintenance could be continued on the average dose of 0.5 mg. daily.

Case 6. This patient was a 65 year old Caucasian male with rheumatic heart disease, cardiac enlargement Grade III, auricular fibrillation and mitral insufficiency, and was in Class III-C. He had been in failure for three years. He had been taking digitalis leaf, 0.1 gm. daily, but because of nausea and vomiting and the appearance of ectopic ventricular contractions, it was discontinued for three days. A dose of 0.1 gm. daily was then administered, and at the end of one month the same signs and symptoms returned. Medication was discontinued for one week and then started again at 0.1 gm. daily for six days of the week. This dosage also caused toxicity, and the digitalis was again discontinued for one week. It was next given in a dose of 0.1 gm. every other day. The patient did not manifest toxicity on this schedule, but after two months his cardiac failure increased, and it was decided that the digitalis dosage was inadequate. It was then increased to 0.1 gm. daily, and for four months his failure did not progress, although it improved only slightly. There were no toxic symptoms. Because a more effective therapeutic dosage could not be attained without toxicity, and because his failure was not significantly better on the dosage tolerated, his medication was changed to gitalin. He was given 0.5 mg. daily for 11 months. There were no toxic symptoms, his signs of failure decreased, and control of decompensation became easier.

Comment: This patient presents a different aspect of the digitalis problem. Maintenance doses of the drug were tolerated fairly well, but were not adequate for effective control of failure. Whenever the maintenance dose was increased, toxicity appeared. Hence, of necessity the patient had to be maintained on suboptimal amounts of glycoside. Changing to gitalin led to better control of the congestive failure.

Case 7. This patient was a 60 year old Caucasian female with rheumatic heart disease, right and left ventricular enlargement, mitral stenosis, mitral insufficiency and auricular fibrillation, and was in Class III-D. She had been in failure for 10 years. Her private physician had given her digitoxin, 0.2 mg. daily, for "many months." For one week prior to entry she had complained of nausea, vomiting and severe anorexia. When first seen she was in marked congestive failure. She had stopped digitoxin for one week prior to entry because of the gastric upset. She was redigitalized with 1.0 mg. of digitoxin and maintained on 0.2 mg. daily. After three days of maintenance therapy, intermittent bursts of ectopic ventricular contractions appeared. The drug was decreased to 0.1 mg. daily. However, on this dosage signs and symptoms of increasing failure began to appear. The dosage was then alternated between 0.1 mg. and 0.2 mg. daily. The pulse varied from 104 to 120 beats per minute. After she had been on this dosage schedule for three months it became increasingly apparent that the digitoxin dose which she could tolerate was not adequate for control of heart failure. She was then given gitalin, 1.5 mg. per day for four days, followed by 1.0 mg. daily for two days. With this treatment her heart rate slowed to 66 to 72 beats per minute. For the next three months she was satisfactorily maintained on 0.5 mg. daily.

Comment: This history clearly shows that the amount of digitoxin which this patient could tolerate was insufficient for control of her heart failure. She was satisfactorily redigitalized with a total effective dose of gitalin of 5 mg. and maintained on 0.5 mg. daily, after which her rate was reduced to 66 to 72 beats per minute, the optimum for cardiac efficiency. The ease with which gitalin controlled her failure comfortably and efficiently is in sharp contrast to the pharmaceutic prestidigitation which was previously resorted to in an attempt to arrive at a tolerable though ineffective dose of digitoxin.

Case 8. This patient was a 52 year old Caucasian male with rheumatic heart disease, cardiomegaly Grade II, auricular fibrillation, mitral stenosis and mitral insufficiency, and was in Class III-C. He had been in failure for 17 months. Three grains of digitalis daily were required to maintain effective control of his failure. He then began to complain of frequent "upset stomach." The drug was changed to digitoxin, with an alternating 0.1 and 0.2 mg. daily maintenance dose. After two months nausea became very severe. Digitoxin was decreased to 0.1 mg. daily for the following two months. At this time congestive failure increased and rehospitalization was necessary. He was given gitalin, 0.5 mg. four times daily for two days, then 1.5 mg. daily for six weeks, followed by 1.0 mg. per day with 1.5 mg. every third day. His failure was well controlled without toxicity for two months. At that time he died from a cerebral embolus.

Comment: The course of failure in this patient was similar to that of case 7, except that he required larger doses of gitalin to regulate his heart

beat and control the failure. He was able to tolerate this unusual amount of glycoside without difficulty.

Discussion

In 1951, Batterman, DeGraff and associates published the results of their four year study of gitalin in which they stressed the wide margin which separated the effective therapeutic dose from the toxic dose.[8] By comparing the average therapeutic (digitalizing) dose of a glycoside with the toxic dose, they arrived at a therapeutic ratio $\left(\frac{\text{therapeutic dose}}{\text{toxic dose}} \times 100\right)$. When digitalis leaf, digitoxin or Digoxin was used they discovered that two thirds of the toxic dose was required to achieve digitalization. In contrast to this, the usual patient required only one third the toxic dose of gitalin, leaving a margin of safety of over 60 per cent. This margin of safety was found to be present not only during initial digitalization with gitalin but also during subsequent maintenance therapy.

The wide margin of safety may explain why gitalin was effective in the eight cases of Group III in this series. Once the narrow margin of safety was exhausted in the case of digitalis leaf, digitoxin and Digoxin, toxicity appeared at a dosage level which was inadequate. The toxic state prohibited further increase in dose, and at the same time further aggravated congestive failure by its deleterious effect on the myocardium.

Gitalin, because of its greater range of safety, was substituted in these cases with efficiency and tolerance. It is of interest that the amount of gitalin required was in many instances average. It was large in one patient, but nonetheless failed to produce toxicity.

The value of the drug in cases of digitalis intolerance has also been demonstrated by Batterman and associates,[10] Hejtmancik and Herrmann,[11] and Haring and Luisada.[12]

Regarding digitalis dosage, it has been stated: "The amount of a digitalis preparation required for satisfactory therapeutic effect cannot be predicted in advance. It must be attained for each individual patient by a trial and error procedure which resembles in many respects a chemical titration for determination of the end point. This end point is the restoration of myocardial efficiency." [10] The results presented in this paper confirm this tenet of digitalis therapy.

As in the case of other digitalis preparations, the "slow" or "rapid" procedure may be followed during digitalization with gitalin. In the "rapid" method, Batterman and associates advised that, to achieve optimal effects, relatively large amounts of the drug be administered over a period of 24 to 48 hours. They recommended an initial dose of 2.5 mg., followed by 1.0 mg. every six hours thereafter until therapeutic effect or toxicity appeared. Digitalization was achieved with an average dose of 6 mg.

An alternative method used by the present investigators for rapid digitalization consisted of 1.0 mg. every four or six hours, with therapeutic effect attained in 24 to 48 hours. This yielded an average digitalizing dose of 6.5 mg., which is similar to that of Batterman and associates.

Hejtmancik and Herrmann, using the oral preparation, also concluded that the "average" digitalizing dose was 6.5 mg. It is of interest that Haring and Luisada, using intravenous gitalin, arrived at a similar therapeutic dose of 5.0 to 6.0 mg.

The "slow" method advocated by Batterman consisted of a single dose of 1.5 mg. daily for four to six days. Some of the patients in this study received the same amount of total daily dose, but in three doses of 0.5 mg. each. Digitalization was obtained in four to seven days. The "average" therapeutic dose with this method was somewhat higher, i.e., 7.0 mg. As explained previously, however, the computation of total effective therapeutic dose with small daily doses over a period of four to seven days, based on the subtraction of 0.5 mg. from the total daily dose after the first 48 hours, may be open to question because of the relatively small dosage given over a relatively longer period of time. Final studies on dissipation of the drug are to be reported.[8] In a series of 44 patients given gitalin for full digitalization, Hejtmancik and Herrmann, using this method of computing dosage, found that 19 patients required 70 mg. and 11 patients required from 7.5 to 9.0 mg. This compares favorably with the studies presented here.

Investigation of effective maintenance dose revealed that 78 per cent of the 45 patients studied could be controlled on a daily dose of 0.5 mg. This is almost identical with the report of Batterman and his group of 79 per cent efficacy with this amount of maintenance gitalin.[10] Sixty-three per cent of the patients of Hejtmancik and Herrmann were maintained on this dose.[11] In changing a maintenance dose of 0.1 gm. of digitalis leaf or 0.1 mg. of digitoxin to gitalin, a dose of 0.5 mg. daily of the latter sufficed in most instances.

Despite unusually large doses used in some instances, no toxicity was encountered among any of the groups in this series. Toxic signs and symptoms due to this drug were studied by other investigators in carefully induced toxic states in attempts to reach full digitalization, and were found to be similar in type to toxicity caused by other digitalis preparations.[10, 11] In 20 of 30 instances of toxicity there appeared various combinations of nausea, vomiting, diarrhea and anorexia, all significant warning symptoms. In 17 of the same 30, disturbances in rhythm and the conduction mechanism of the heart appeared. The duration of toxicity was far less than with digitoxin or digitalis leaf.[11]

Summary

1. Amorphous gitalin was used in the treatment of congestive heart failure of varying causes, degrees and duration in 68 patients.

2. Gitalin was safely, comfortably and effectively useful in initial digitalization, redigitalization and maintenance digitalization of patients in heart failure.

3. Case reports have been presented in which gitalin was of value in promptly and safely establishing digitalization and control of heart failure in eight patients in whom digitalis, digitoxin and Digoxin were ineffective due to toxicity.

4. No toxicity was encountered in any patient studied in this series.

5. The clinical application of the wide difference between toxic and therapeutic dose in gitalin is an important advance in the pharmacology of cardiac glycosides.

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THE USE OF ANGIOCARDIOGRAPHY IN THE SELECTION OF PATIENTS FOR MITRAL VALVULAR SURGERY *

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THE best results of mitral valvular surgery have been obtained in those patients with mitral disease characterized chiefly by stenosis. As yet, we consider surgery for correction of mitral insufficiency to be in the preliminary stage of its development, although much work has been done on this problem. It is desirable, therefore, to choose for surgery those patients with mitral obstruction of a degree sufficient to prevent satisfactory diastolic filling of the left ventricle. Ordinary methods, including the routine history, physical examination and standard roentgenographic technics, have been inconsistent in predicting the degree of mitral valvular obstruction. Hence, the search for significant data has led to the use of various special studies intended to clarify the hemodynamic status in patients with mitral disease. We have found angiocardiography of great value in the recognition of patients with a state of predominant mitral stenosis who would qualify well for surgery.

Initially our angiocardiographic studies of patients with mitral stenosis were begun in the hope that we might identify pulmonary vascular changes secondary to mitral disease.[1] The possibility that such changes could produce circulatory obstruction in the lungs of greater degree than that present at the mitral valve seemed an important problem. We felt that alterations in the timing of opacification might provide useful information relative to the site of circulatory obstruction in such patients. Preliminary findings proved of sufficient interest that more detailed studies by angiocardiography were undertaken.[2, 3] Our studies were concerned with the physiologic as well as the anatomic changes demonstrable by angiocardiography. This in itself was not an entirely new concept. Robb and Steinberg recognized that angiocardiography provided a method whereby the circulation time to various parts of the cardiovascular system could be determined objectively, and pointed out that their technic opened a new field for investigation of both the anatomy and the physiology of the circulation.[4] However, in a subsequent study that included six patients with mitral stenosis and insufficiency, they were concerned chiefly with the anatomic aspects of determining the component parts of the cardiac silhouette in heart disease.[5] Another report of the angiocardiographic findings in mitral stenosis also dealt pri-

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marily with an analysis of the cardiac configuration from the anatomic viewpoint, although it indicated a realization of physiologic concepts in a brief statement to the effect that "the altered hemodynamics in mitral stenosis resulted in stasis in the left atrium with prolonged and intensified opacification." [6] None of these earlier studies, of course, included correlation of the angiocardiographic findings with the findings at operation, and there has been no recent general appreciation of the degree to which angiocardiography might prove helpful in the preoperative study of patients with mitral disease.

Technic *

The technic used in this study was essentially that originally described by Robb and Steinberg,[4] with certain important modifications:

1. A large vein in the right antecubital space was surgically exposed and the Robb-Steinberg cannula was tied in place.

2. With 3 c.c. of 20 per cent sodium dehydrocholate diluted to 50 c.c. volume, an arm-to-tongue (Decholin) test was done. Both the arrival time and the disappearance time were used to select the best intervals for exposure of films. With this preliminary information the films could be appropriately spaced throughout the entire period the opaque material remained in the heart and great vessels.

3. A seven film cassette-changer was preferred over the roll-film type of camera, since this permitted the use of large 11 × 14 films.

4. The patient was placed in the left lateral recumbent position with the right shoulder slightly anterior to the left shoulder. Since the film is just beneath the table top, the position results in a left anterior oblique exposure about 15 degrees away from the full lateral position.

5. When intervals between films were longer than 3 seconds, the patient was instructed to breathe one or more times. This maneuver required coaching throughout the procedure.

6. Preliminary scout films were taken the day before angiocardiography to assure proper positioning of the patient, and proper exposure factors in the films.

Choice of Patients

We deliberately did not subject normal persons to this procedure because adequate control studies were available from a large group of patients without valvular heart disease who had other conditions requiring angiocardiographic study. The initial studies in mitral disease were made on a group of patients considered on clinical grounds to have so-called "pure" mitral stenosis. On auscultation each showed a loud apical diastolic rumbling murmur with little or no systolic murmur. Electrocardiograms and roent-

* After preliminary sensitivity tests, 50 c.c. of either 70 per cent Diodrast or 75 per cent Neo-Iopax were injected intravenously as the contrast substance.

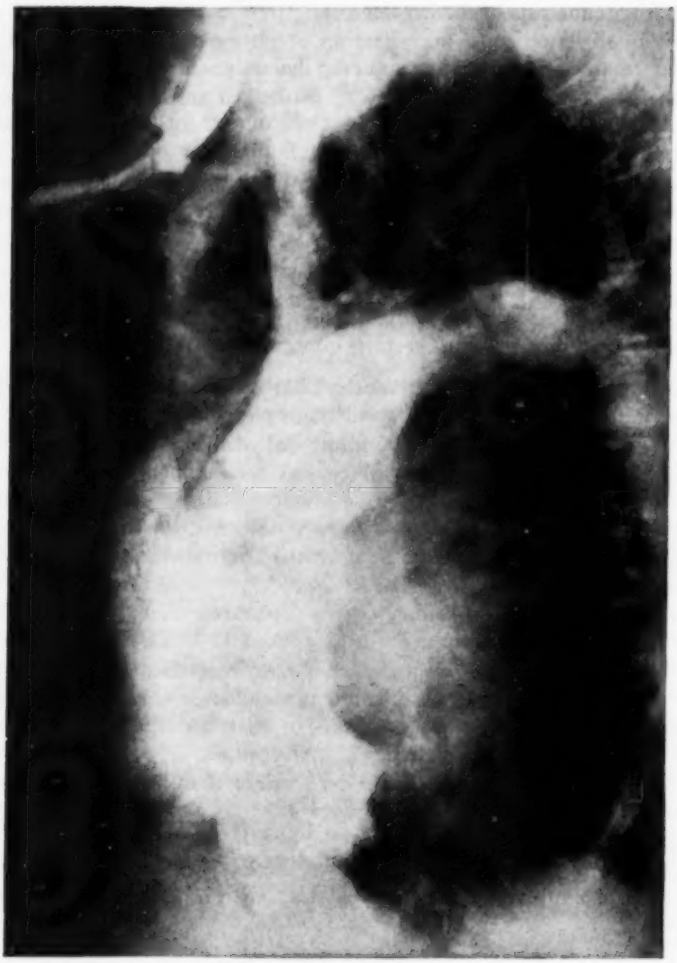


FIG. 1. Angiocardiogram taken 2 seconds after injection of opaque material. Patient with typical physical signs and standard roentgenographic findings of "pure" mitral stenosis. Diagnosis confirmed at operation. Film shows opacification of right heart and pulmonary arterial system.

genographic findings were considered compatible with uncomplicated mitral stenosis. The next phase of the study included a group of patients considered on clinical grounds to have major mitral insufficiency. On auscultation, each patient had a loud apical systolic murmur with little or no mitral diastolic murmur. Other findings were considered compatible with major mitral insufficiency, including standard roentgenograms which were

interpreted as showing left ventricular hypertrophy. Subsequently, when it appeared that angiocardiography might be of value as a routine procedure, a large group of patients with mitral disease who were being evaluated as candidates for mitral commissurotomy were studied angiocardiographically. In all, a total of 150 patients was studied.

FIG. 2. Same patient as figure 1. Angiocardiogram 8 seconds following injection. Note the dense and sharp opacification of the left atrium. The left ventricle and aorta are poorly opacified in comparison. The pulmonary veins are also prominent.

RESULTS

A. In patients without valvular heart disease, the angiocardiogram was characterized by opacification in normal sequence of the cardiac chambers, beginning with the right atrium and progressing rapidly through the other chambers. The right side of the circulation as a unit usually showed

maximal opacity within two seconds after the injection and faded out within six seconds on the average. The left side of the heart began to show opacification within four or five seconds, became maximally opacified at eight to 10 seconds, and was clear of opaque material within 12 seconds or less after the injection. It must be emphasized that the opaque material passed quickly and freely from one chamber to the next in patients without

FIG. 3. Same patient as figures 1 and 2. Angiocardiogram taken 18 seconds following injection. Left atrium still sharply opacified in contrast to left ventricle and aorta.

valvular disease. Thus, on returning from the lungs to the left heart, the opaque substance usually opacified the entire left heart as a unit, promptly and with fairly uniform density.

B. In those patients with so-called "pure" mitral stenosis, a characteristic change in the angiocardiogram occurred. Whereas patients without valvular disease showed a rapidly progressing and uniform opacification of

the left heart, those with mitral stenosis showed a prolonged and dense opacification of the left atrium. Furthermore, the left ventricle was never opacified to a degree equal to the left atrial density. This typical pattern is demonstrated in figures 1, 2, 3 and 4. These figures show that in mitral stenosis the left atrium became very densely opacified, while the left ventricle

FIG. 4. Same patient as in preceding figures 1, 2 and 3. Film taken 28 seconds after injection. Left atrial opacification fading, but still retains a slight contrast with other chambers.

was poorly opacified. The opaque material seemed to "hang up" for abnormally long periods within the left atrium.

C. It was expected that patients with so-called "wide-open" mitral insufficiency would not show this difference in opacification between the left atrium and the left ventricle. Rather, we anticipated that with predominant insufficiency the mixing of opaque material between the two chambers of the

left heart would be fairly uniform. Actually, many of those deliberately selected on clinical grounds to form a control group of patients with major mitral insufficiency showed exactly the anticipated picture, namely, enlargement of both the left atrium and the left ventricle, but with no sharp differentiation of their opacity. However, we found that several patients of this group diagnosed clinically as having predominant mitral insufficiency showed angiocardiograms previously found to be typical for mitral stenosis. Mitral commissurotomy was performed in five such patients. Despite the absence of an apical diastolic murmur, and despite the clinical picture of major mitral insufficiency, they were found at operation to have major correctable mitral stenosis.

Discussion

The series of 150 patients with mitral disease studied by angiocardiography is analyzed in table 1. Of these patients, 123 were operated upon (119 here and four elsewhere), with 17 deaths (12 autopsies), for a total

Table I

Clinical Classification		Surgery Recommended		Candidates Rejected after Angiocardiography	Classification at Surgery	
		Accepted by Patient	Postponed by Patient		Mitral Stenosis with Little or No Regurgitation	Adequate Opening with Prominent Regurgitant Jet
"Pure" mitral stenosis with little or no systolic murmur	62	60	2‖	0	60	0
Loud apical systolic murmur raising the question of mitral insufficiency	88	63	9	16	57*	6†
Total	150	123	11	16	117	6

* Includes 5 patients with no apical diastolic murmur.
† Discussed further in paragraph 4 of Discussion. Five of the six had good results following surgery.

mortality of 14 per cent. Twenty-seven patients were not subjected to operation; of this group, 16 were rejected as candidates after angiocardiographic study, while 11 were advised to have operation, but postponed or refused surgery. Six of these 11 have since died (three autopsies).

Correlation of the angiocardiograms with the condition of the mitral valve as determined at operation or autopsy demonstrated two angiocardiographic findings to be characteristic of mitral stenosis: first, the sharp outline of the left atrium due to obviously greater opacification of the left atrium than the left ventricle; and second, the persistence of this differential opacification for abnormal periods of time. The significance of these findings warrants further discussion from several points of view.

1. The Cause of the Difference in Chamber Density: The cause of the difference in opacification of the left heart chambers is not entirely clear to us. We do not know whether the actual concentration of opaque material differs as much in the left atrium and left ventricle as the angiocardiographic appearance suggests. The phenomenon might be related to the relative depth of the two chambers as viewed in the left anterior oblique position. It is to be emphasized that all our studies were made with the patient in a left anterior oblique position approaching a lateral view. We have had very little experience with anteroposterior projections, and are not prepared at this time to say whether the criteria can be applied to such studies.

2. Factors Affecting Duration of Opacification: The duration of left atrial opacification apparently bears a relationship to the left atrial size and cardiac size, and to the presence or absence of auricular fibrillation. More detailed analyses of these hemodynamic factors will be presented elsewhere, but in general, the duration of opacification was longer in patients with larger hearts or with auricular fibrillation and shorter in those with smaller hearts and normal rhythm.

The duration of left atrial opacification may be prolonged in the presence of either mitral stenosis or mitral insufficiency, and the absolute time in itself is not differentially diagnostic. The angiocardiographic diagnosis of predominant mitral stenosis requires that the left atrium become opacified more densely than the left ventricle, so that the atrium becomes sharply outlined by contrast. When this difference of opacity of the left heart chamber was present, its duration often was variable in patients with openings of similar size at the mitral valve. The duration of sharp atrial contrast in itself was of less significance than its relationship to the total time necessary for clearance of all opaque material through the heart. For example, a difference in the opacification of the left atrium and left ventricle lasting only three or four seconds out of a total passage time of 12 seconds might indicate significant stenosis in a patient with a small heart and normal sinus rhythm. In patients with larger hearts and auricular fibrillation the total time from injection to clearance may be much longer, and we have not uncommonly seen atrial opacification remaining for 45 seconds and occasionally for 75 seconds.

3. Significance of Chamber Size: Enlargement of the left ventricle has commonly been considered to represent a further indication of the presence of significant mitral insufficiency in those patients with prominent apical systolic murmurs. However, the diagnosis of left ventricular enlargement by standard roentgenographic methods has been difficult and not entirely dependable. Angiocardiography permits more accurate determinations of chamber size, in addition to the information provided by alterations in timing and degree of opacification. In general, it has been found that the left ventricle has usually appeared large in those angiocardiograms showing the uniform opacification of the left heart chambers characteristic of mitral in-

sufficiency. Conversely, the left ventricle has been relatively small in those angiocardiograms showing the marked difference in opacification of the left heart chambers which has been considered characteristic of predominant mitral stenosis.

In patients with mitral stenosis, the left atrium is so sharply outlined during angiocardiography that its size can be determined easily. However, atrial size considered alone was of no value in the differentiation of predominant mitral stenosis from predominant mitral insufficiency because the left atrium was enlarged in all the patients with mitral disease that we studied. Thus the differentiation required the application of other criteria, as discussed above. We were unable to determine any special significance in the degree of left atrial enlargement, with the possible exception that those patients with so-called giant left atria usually were found at operation to have a palpable regurgitant jet in addition to their mitral stenosis.

4. Reliability of Auscultation: From these studies we have learned that auscultation alone frequently can be misleading in the evaluation of patients for mitral commissurotomy. Auscultation proved most reliable in those patients with so-called "pure" mitral stenosis who had loud apical diastolic murmurs but in whom apical systolic murmurs were either absent or faint. Sixty of the 123 patients who were operated upon had auscultatory findings of this type and were found at operation to have mitral stenosis with little or no palpable insufficiency. Such patients could probably be referred safely for operation on clinical grounds alone, without subjecting them to angiocardiographic study. On the other hand, the absence of an apical diastolic murmur does not rule out the presence of mitral stenosis. As noted above, five such patients have been referred for surgery on the basis of their angiocardiographic findings when definite auscultatory evidence of mitral stenosis was lacking. They were found to have tight mitral valves with little or no regurgitant jet.

Auscultation is particularly unreliable in evaluating the group of patients with loud apical systolic murmurs. Of the 150 patients in this study, 88 had prominent apical systolic murmurs which raised the question of predominant mitral insufficiency. Only 16 of these patients (18 per cent) were rejected for operation because their angiocardiograms were considered to indicate the presence of predominant mitral insufficiency. The remaining 72 patients (82 per cent) showed the angiocardiographic findings characteristic for predominant mitral stenosis. Nine of these were in the group of 11 patients who did not come to operation; six of this group died, and the three patients for whom autopsy consent was obtained showed mitral stenosis. Sixty-three patients accepted the recommendation of surgery, and 57 of them were considered at operation to have mitral stenosis without significant regurgitation. In each of the remaining six patients, the mitral valve was considered by the surgeon to have an adequate original opening (at least two fingersbreadth), together with a prominent regurgitant jet. However,

in five of these patients the opening was significantly increased (at least one additional fingerbreadth), and the patients subsequently were found to be improved. The other patient was one of those having a giant left atrium, and in this instance a separate left ventricular shadow had not been identified on the angiocardiogram. This patient is discussed further under "False Results."

5. *A Proposed Concept:* From our studies we have been tempted to adopt a concept of "functional stenosis," and consider that the absolute anatomic size of the mitral orifice alone is not of the importance some might believe. An opening that would be adequate in a patient with a small heart and normal rhythm could well be inadequate in a patient with a greatly enlarged heart and auricular fibrillation. Calculating the absolute area of the mitral opening may be less valuable than knowing whether the left atrium can empty effectively.

This concept of "functional stenosis" leads further to a questioning of the current acceptance of the surgeon's finger as the final court of appeal in

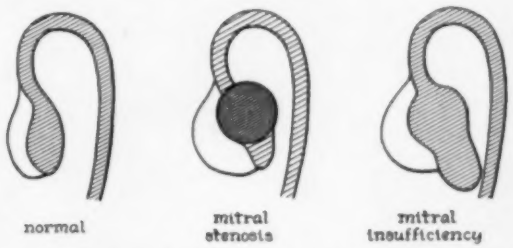


FIG. 5. Diagrammatic illustration of characteristic left heart opacification patterns in patients without valvular heart disease, those with "pure" mitral stenosis, and those with "wide-open" mitral insufficiency. Note sharp difference in opacification of left atrium and left ventricle in patients with mitral stenosis as contrasted with the uniform opacification of the left heart in normals or in mitral insufficiency.

the diagnosis of mitral stenosis and insufficiency. We have discussed certain patients with a "positive" angiocardiographic test for mitral stenosis in whom the surgeon has described at operation the presence of an adequate opening in the valve, together with a prominent regurgitant jet. However, the opening was further enlarged by mitral commissurotomy and the patients subsequently were much improved by the procedure. Several of our outstandingly good results occurred in such patients. Blood flow through the valve is not only a function of the resistance offered by the contracted orifice but also of the pressure relationships between the two chambers. Pressure relationships in turn depend on other factors such as chamber size, arrhythmias and myocardial integrity. The surgeon's appraisal of a valvular opening by palpation does not include such determinations of flow and pressure relationships.

Perhaps in the final analysis our thinking should not be directed toward "stenosis" and "insufficiency" in their anatomic connotations but rather toward the total functional effect of these lesions upon the left atrial emptying and left ventricular filling. In our opinion, this functional abnormality has usually been demonstrated well by angiocardiography. When the angio-

FIG. 6. **Angiocardiogram taken 16 seconds after injection. Patient with clinical and standard roentgenographic findings of "pure" mitral stenosis. Note sharp opacification of left atrium and large pulmonary veins. The left ventricle is small and poorly opacified. Patient found at operation to have "pure" mitral stenosis and findings further confirmed at autopsy.**

FIG. 7. Angiocardiogram taken 15 seconds after injection. Patient with clinical and standard roentgenographic findings of "pure" mitral stenosis. Operation recommended but postponed. Autopsy confirmed presence of severe mitral stenosis. Note sharp opacification of left atrium and large pulmonary veins. The right heart has remained unusually well opacified for this period of time; this finding suggests impairment of blood flow through the right heart and pulmonary circulation.

cardiogram was considered "positive," patients usually improved if the opening of the mitral valve was increased by surgery. This improvement was often independent of the surgeon's estimate of the initial degree of stenosis and the presence or absence of a regurgitant jet.

6. Borderline Results: The angiocardiographic findings characteristic

for "pure" mitral stenosis and "wide-open" mitral insufficiency have been described above. These two distinctive patterns of left heart opacification are illustrated diagrammatically in figure 5. One might of course anticipate that varying degrees of mitral stenosis and insufficiency in combination could produce gradations between the angiocardiographic patterns typical

FIG. 8. Angiocardiogram taken 9 seconds after injection. Patient did not fall into category of those with "pure" mitral stenosis as classified by clinical and standard roentgenographic methods. Note dense opacification of left atrium. However, left ventricle is larger and slightly more opacified than those illustrated in figures 6 and 7. At operation patient was found to have mitral stenosis with no regurgitant jet. This angiocardiographic pattern nears the borderline between acceptability or rejection for operation.

FIG. 9. Angiocardiogram taken 17 seconds after injection. Patient with prominent apical systolic murmur. At operation a slight regurgitant jet was palpated and the valve opening was estimated to be almost two fingersbreadth. Note that in the photograph, the left atrium and left ventricle approach equality of opacification although a slight difference was apparent in the films from which the photograph was made. This is a borderline angiocardiogram and the findings at operation were of borderline type. Unfortunately technical difficulties at operation prevented the surgeon from further widening the valve, so that the patient could not be improved. However, others with similar findings were improved when further widening was possible. This case illustrates the difficulties of interpretation in borderline films.

for either lesion alone. We have found examples of such gradations in various patients ranging from those considered most suitable for operation to those who were rejected. Selected angiocardiograms illustrating these

various gradations are shown in figures 6, 7, 8, 9 and 10. Borderline angiocardiographic findings such as those shown in figure 9 made it difficult to decide whether the patient should be advised to have an operation. While such difficulty can arise in the occasional borderline test, the decisive nature of the pattern when the angiocardiogram is typical for either "pure" mitral

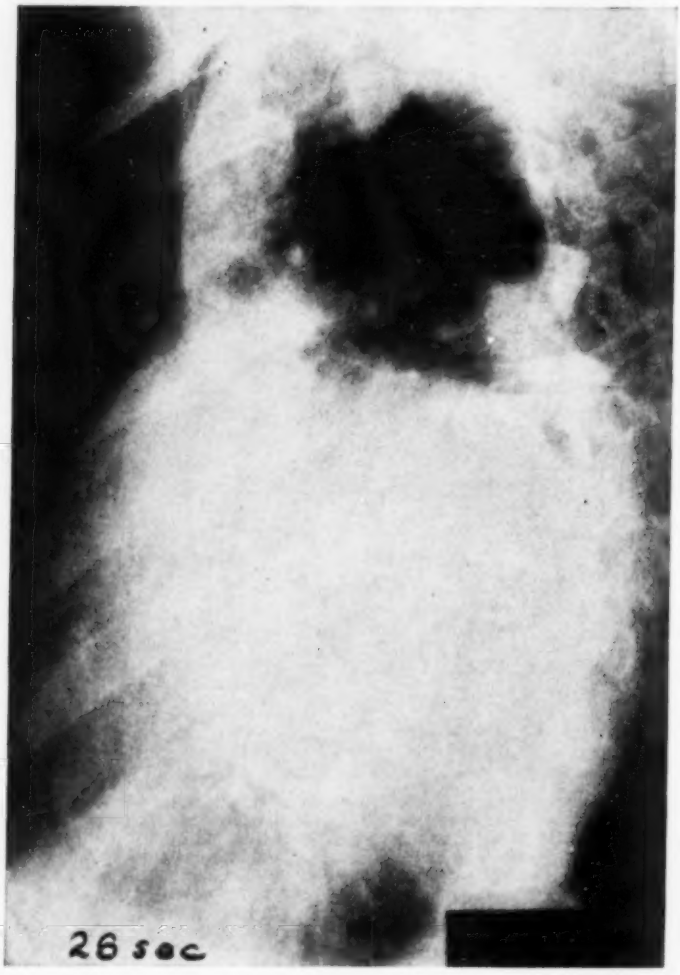
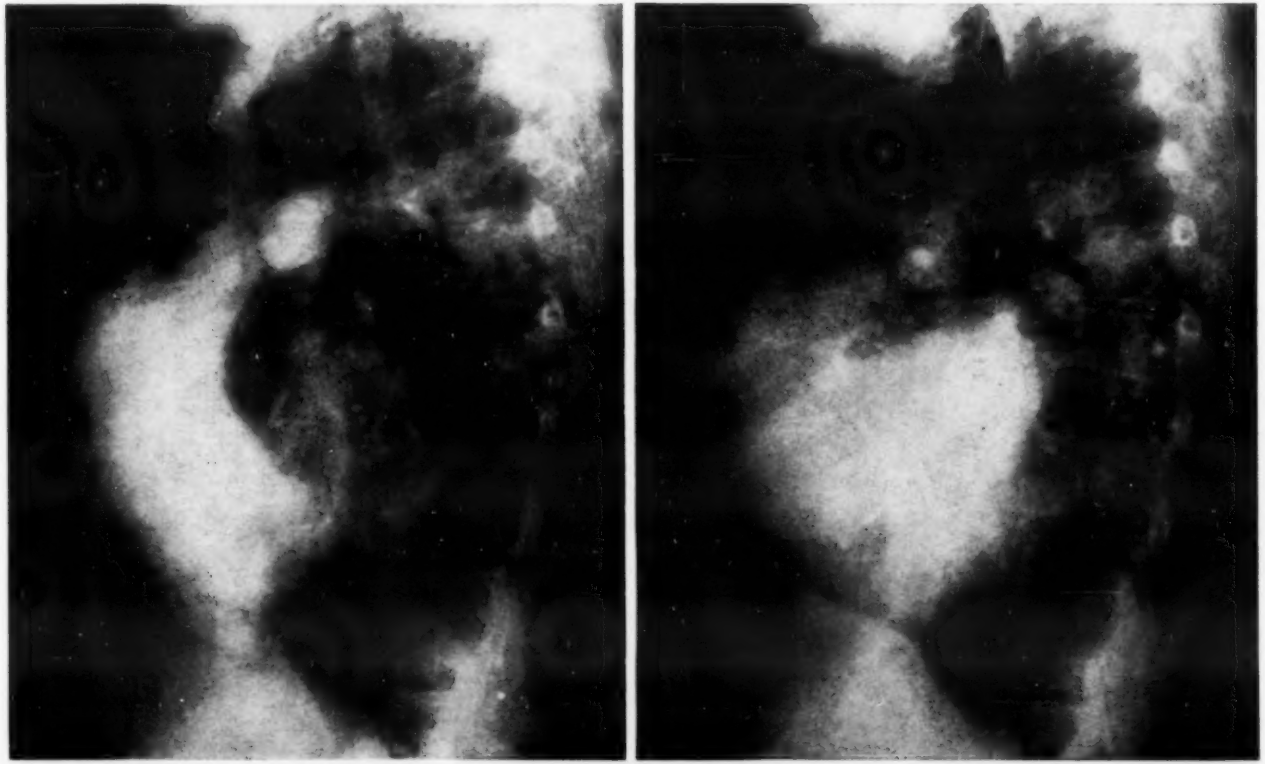


FIG. 10. Angiocardiogram taken 26 seconds after injection. Patient was believed to have predominant mitral insufficiency on basis of clinical findings and routine roentgenologic methods. Note the enlargement of left atrium and left ventricle, with uniform opacification of both chambers. These findings were interpreted as indicating major mitral insufficiency and patient was rejected as candidate for surgery.



A B

FIG. 11. Film A was taken at 2 seconds and Film B at 16 seconds after injection. Patient had classical findings of mitral stenosis clinically. Left atrium is outlined by opaque material, but is not so dense as one might have anticipated from physical signs. At operation patient had tight mitral stenosis but also a large clot filling the left atrium.

FIG. 12. Angiocardiogram taken 18 seconds after injection. Patient with questionable diagnosis on clinical basis. Left atrium outlined as in "positive tests" for mitral stenosis. However, presence of calcified pericardium raised question of whether apparent left ventricular shadow was actually left ventricle or thickened pericardium. At operation patient proved to have mitral stenosis in addition to calcific pericarditis.

stenosis or "wide-open" insufficiency is of great value in the preoperative evaluation of patients with loud apical systolic murmurs.

7. "False" Results: So far, angiocardiography has given excellent results in our hands, but we realize that few medical tests prove to be 100 per cent reliable. We can recognize certain situations which could lead to "false-positive" or "false-negative" results:

(1) *A "false-negative" test* means the failure to recognize mitral stenosis when it is actually present. In our experience the commonest cause of this has been the presence of a large clot filling the left atrium so that this chamber could not show its expected dense opacification. Figure 11 shows the

angiocardiogram of a patient with definite mitral stenosis as diagnosed on clinical grounds, but in whom the angiocardiogram failed to show the usual sharp contrast in opacification of the left atrium and ventricle. At operation this patient was found to have mitral stenosis but also a large clot filling the left atrium.

Other potential causes of poor left atrial opacification in the presence of mitral stenosis include slowness of the initial injection so that the opaque material becomes diffused and fails to travel as a bolus. Similarly, one might expect that severe pulmonary vascular changes could slow the passage of the opaque medium through the lungs and interfere with opacification of the left atrium, although in our experience this has not been a cause of difficulty in interpretation.

(2) *A "false-positive" test* means the diagnosis of mitral stenosis by angiocardiography when the valve actually is not stenotic. Within the limits of our present experience, we believe this error could arise only if some other shadow were mistaken for the left ventricle when a separate and less opacified left ventricle was not demonstrated. This question was raised, for example, when the presence of a thickened pericardium was considered possible in one patient. (See figure 12 and legend.)

A corollary difficulty arises when no separate left ventricular shadow can be identified. Under such circumstances one cannot determine the relative opacification of the left atrium and ventricle. This difficulty of interpretation occurred in one patient in whom the left ventricle was completely obscured by a markedly dilated left atrium. We were aware preoperatively that no separate left ventricular shadow had been identified, and considered the results of the angiocardiographic study to be inconclusive. As described above in paragraph 4, the patient was found at operation to have an adequate opening of the mitral valve, together with a regurgitant jet. A significant increase of the valve opening was not produced, and the patient has not been improved following surgery.

It must be emphasized that simply demonstrating the left atrium to remain densely opacified for prolonged periods does not constitute a "positive" test unless the left ventricle can also be recognized and can be seen to be less densely opacified than the atrium.

Summary

1. An angiocardiographic study of 150 patients with mitral disease has been made. The condition of the mitral valve was determined at operation in 123 of these patients.

2. A characteristic angiocardiographic pattern was demonstrated in those patients who were found at operation to have significant mitral stenosis with little or no regurgitant jet.

3. The study included 62 patients with typical clinical findings of "pure" mitral stenosis. Sixty of these patients came to operation and were found

to have mitral stenosis. In these patients, angiocardiography showed the pattern characteristic for mitral stenosis, although it was modified to varying degrees in a few patients with left atrial clots. While angiocardiography readily confirms the diagnosis in this group of patients, it is not an essential preoperative study, since clinical diagnostic error is unlikely and operation can be recommended justifiably on clinical grounds alone.

4. Also included were 88 patients who had prominent apical systolic murmurs and were suspected of having significant degrees of mitral insufficiency. Of these patients, only 16 (18 per cent) were rejected as candidates for surgery because their angiocardiograms were considered characteristic for "wide-open" mitral insufficiency. In the other 72 (82 per cent) the angiocardiogram was considered characteristic for predominant mitral stenosis. Angiocardiography has proved very helpful in the preoperative evaluation of this group of patients with loud apical systolic murmurs. It may establish the diagnosis of mitral valvular obstruction when the clinical findings make such a diagnosis difficult or uncertain; for example, in five patients mitral stenosis was shown to be present when no diastolic murmur could be heard.

5. Our experience indicates that patients with the characteristic angiocardiographic pattern of mitral stenosis have an excellent chance for surgical improvement despite the fact that auscultation may suggest the presence of predominant mitral insufficiency. Furthermore, significant improvement has followed valvular surgery in five patients despite the initial estimate by the surgeon of an adequate valvular orifice together with a prominent regurgitant jet. The surgeon should be urged to widen such valves further if possible when the preoperative angiocardiogram has indicated impairment of left ventricular diastolic filling.

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AN ETIOLOGY OF SCLERODERMA *

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When the etiology of a disease is unknown its treatment is at best haphazard. This has heretofore been the fate of Raynaud's disease and scleroderma. From an analysis of clinical material,[5] we concluded that the vasospasm of minute vessels which characterizes Raynaud's disease is the somatic manifestation of a chronic psychologic derangement. This viewpoint has since found support.[3, 9] At that time evidence was available that scleroderma had the same origin. We now present analyses of our clinical findings which make more evident the relationship of Raynaud's disease to scleroderma. They are one disease, and differ only in the intensity and extent of their pathology. A definite time relationship exists between the onset of scleroderma and an incident in the patient's life situation which initiated a threat to his personal security. The basic personality always has been one of commensalism as described for Raynaud's disease, but more inflexibly so. Reëstablishment of this type of security alone can end the active phase of the disease and permit therapy to be efficacious or unnecessary. Sympathectomy or the use of vasodilating drugs before this has occurred can at best develop transient (but never permanent) vasodilatation; but more often, by their failure to help, they may aggravate the disease.

Patient Material: Seven patients were studied and treated. Repeated medical examinations revealed no infectious or allergic cause for small vessel disease. No large artery or vein was found involved on physical examination and biopsy (or necropsy, when performed). Our case reports record the salient medical and psychologic features chronologically. Specific diagnostic procedures, when performed, are included, and their significance is developed under discussion.

Case Reports

Case 1. (1933.) A 21 year old male came to the clinic complaining of cold hands and feet which had paled when chilled and flushed and burned when warmed for the past two years. Of late they remained cyanotic for long intervals.

(1934–1935.) Color changes were more severe and fingers ulcerated. Psychiatric studies reported that the patient lacked energy and persistence. His inability to stay on a job for the past few years was considered significant. Social worker found his parents inadequate in their relationship to society.

Bilateral sympathectomies were performed at D_1 and D_2. The postoperative course was complicated by a pneumothorax.

(1935–1936.) Ulcerations were still troublesome and color changes were marked. Electrocardiogram showed abnormal T_3.

(1936–1937.) Face showed evidence of scleroderma. The psychiatrist elicited the following history: In 1931, at an age when the patient's friends were obtaining

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jobs, he was unable to find work. He was lonely and disappointed. He could not keep up with his friends financially and therefore socially. He was disturbed because life went on about him, although people were dying. The examiner felt that he had a "schizophrenic type of anxiety."

(1937–1938.) For the first time since the onset of his illness there were no open wounds on his fingers. He bruised easily but the skin was supple and healed. He was working regularly, had money and was able to go out and keep up with his friends.

(1939–1940.) Physical and economic improvement was being maintained.

(1941–1942.) Vascular status regressed sharply; scleroderma of face and hands was marked. Medical examinations because of eructations and diarrhea were unrevealing. Blood pressure was normal. He lost his job late in 1940 and since then has worked irregularly.

(1943.) Admitted to the hospital because of hypertensive encephalopathy, he died in uremia. Necropsy was grossly negative. Hyalinization of the intima with fibrosis of the small arteries and arterioles was found in the kidneys, liver, myocardium and lung on microscopic examination.

Summary: The patient was an untrained youth, living in an insecure home. Dominant themes in his personality were death and insecurity. He developed Raynaud's disease and later scleroderma, cutaneous and visceral, during a period in which this loneliness was intensified. He lost all his boyhood friends when they began to earn money and he could not get a job. Sympathectomy during this period was of no avail. Only during a wartime labor shortage, when everybody was working, did he earn money. During these two years he improved markedly. His prosperity over, scleroderma recurred, with lethal sequelae.

Case 2. (1938.) A 45 year old female noted for the first time that the skin of her arms, hands and face was taut. Her hands changed color promptly with every change in temperature. Her heart pounded. Summer warmth relieved her.

She had been born in Poland and raised in a well-to-do household. When her father died she left college and married a government official. Sensing the oncoming Nazi terror, he left Poland to find a safe haven for the family. As soon as he left she developed the symptoms described above.

(1939–1942.) Her symptoms and signs were completely relieved as soon as she was able to join her husband, who had preceded her and settled in the United States.

(1943–1944.) Symptoms recurred; the skin of her fingers and face became taut. The tips of her fingers had shrunken so that only half of the nail was now visible.

Her husband had developed coronary thrombosis and a few months later was dead. Without funds, she was forced to work in a factory, painting dolls and toys until her ulcerated fingers became useless and she had to leave.

(1945.) Seen for the first time, she presented the typical picture of advanced scleroderma of hands, arms, fingers and face. Studies of pulmonary function made at the time were considered by the examiner to be characteristic of scleroderma.

The situation was explained to the patient. The social worker interviewed the daughter, who was a college student and supported herself. She refused to assume responsibility for her mother and "pamper her as her father had done." She wanted to live her own life. A compromise was arranged. Her daughter contributed more personal interest and some money. The patient obtained a job which did not require the use of her fingers. She showed great pride (though not without misgiving) in her ability to care for herself. A marked improvement in her face and fingers followed.

Summary: The sudden onset of vasospastic phenomena coincided with the abrupt loss of the security so well provided her by father and husband. Insight and social adjustments have given her a respite from the unrelenting advances of her disease, though protection is still incomplete.

Case 3. (1944.) The 28 year old patient, her husband and three children left New York for California seeking economic improvement. While there she became pregnant. The prenatal period was normal and no drugs were taken. With the onset of labor she entered a local hospital and a series of untoward events followed. Her obstetrician could not be reached and she was delivered by the intern. The following day she bled profusely. The nurse unsuccessfully credéd her uterus, meanwhile screaming for the intern. This went on for some time, until the patient's husband chanced into the hospital and was sent scurrying for the intern. He was located and succeeded in stopping the bleeding. On the fifth day the patient was discharged. The following day her temperature was 105° F. and pain was present in her pelvis and left hip. Frightened, she ran down to a neighborhood telephone and summoned her obstetrician, who said he would be right over but never came. Sick and discouraged, the family packed and trekked back to New York. The patient came to the clinic complaining of backache, weakness of her legs and changes in the color of her hands and feet when cold. She had visited several clinics and doctors and had been told that she was a neurotic.

(1945.) Work-up revealed no visceral involvement. Her skin was taut and gritty when venipuncture was attempted. Color changes typical of Raynaud's disease were present. The facial expression was typical of scleroderma. Vomiting was marked, but x-rays failed to disclose sclerous or other changes in the digestive tract.

The patient's personality and social background were unfolded by psychologic studies. Her intelligence was classified as a dull normal in the lowest third of adult groups. She had a "neurotic state of depression and anxiety. Her concept of life was one of compliance under external pressure. Her spirit had been broken by the beatings of her parents and brothers. Her husband had been a poor provider and she does not feel accepted and protected. She lives in a continuous state of deep anxiety intensified by her disability. The patient would be expected to experience states of fear and dread."

(1945.) Her husband obtained a good job. At our suggestion she was given a weekly allowance. Prompt clinical improvement followed.

(1946.) Improvement maintained; no vomiting; color changes rare.

(1947.) She became pregnant. Her sister-in-law told her that she would die if she did not have this pregnancy interrupted. She was, however, more fearful of the danger of abortion. The manifestations of scleroderma reappeared in full force. Reassurance by the obstetrical staff ameliorated her anxieties and symptoms. Premature separation of the placenta and death of the fetus suddenly ended this phase of her life. Color changes in her hands, though not so intense, were still present in her hands and feet. Permanent changes in circulation due to obliterative changes in the digital arteries were noted. Her husband was still working.

Summary: A susceptible person whose life situations have been characterized by insecurity rapidly manifested severe scleroderma and Raynaud's when death threatened her in childbirth, and again three years later. Relief followed each improvement in her sense of security. Disabilities due to permanent obliterative changes in her small digital arteries persist.

Case 4. (1945.) For the past nine years a 45 year old female had had cyclic episodes of pallor, numbness, rubor and burning of her hands and feet. Six months

before coming to the clinic she had had bilateral sympathectomies in another city, but without benefit. Examination at this time showed severely ulcerated fingers, marked color changes and scleroderma of hands and face.

(1946.) Left lumbar sympathectomy was performed in the same hospital where, on the fifth postoperative day, she had a generalized convulsion. She appeared very ill on her return to the clinic. The scleroderma was very disabling.

(1947.) After a grand mal seizure at home she was admitted to the hospital and died after a few days.

Her significant background had begun 20 years before, when she married a student lawyer against the advice of his family. The responsibilities of marriage and children kept them in a continuous state of insecurity. Her husband's family constantly reminded her that their hasty marriage had prevented his success as a lawyer. With the death of her father nine years ago her symptoms of Raynaud's disease began, and it has progressed rapidly since that time. Though her husband became a post office clerk four years ago, with some security, there was no change in her condition. The operations were paid for by her husband's brothers, and their failure to help depressed her further.

Necropsy revealed "diffuse disturbances in the capillaries and arterioles of all her viscera and brain. Their lumina were narrowed by thrombi secondary to changes in the vessel walls. The intima and to a lesser degree media and adventitia had deposits of pink staining homogeneous material. There were proliferation and fibroses in the subendothelial region."

Summary: The death of her father precipitated the development of her severe vascular disturbance. An insecure marriage and dependence upon well meaning in-laws had prepared her for this response. Sympathectomies hastened rather than abated the disease by their failure to help.

Case 5. (1942–1943.) A 39 year old female for the past year had noted that her fingers turned blue when exposed to the cold and red when warmed. She was referred by her family physician, whose treatment had consisted of many injections. The fingers showed moderate cyanosis and no trophic changes. There was no visceral disease.

Her married life had been an unhappy one. The onset of her illness coincided with her husband's refusal to grant her a religious divorce which would enable her to marry someone whom she "loved and respected." She felt superior to her husband, an accountant. Both were orthodox religious conformists. When the other man, a physician, no longer willing or able to wait, left the city to settle elsewhere, the symptoms of Raynaud's disease became manifest. Her insight was ample, but she could neither accept nor change the life situation which was repulsive to her. The disease progressed rapidly. She did not return to the clinic.

(1943–1944.) She was admitted to another hospital. Scleroderma without visceral involvement was present.

(1944–1945.) Admitted to a third hospital, she was found to have visceral scleroderma. Temperature was elevated. Pericarditis, pleuritis with effusion and azotemia were present. She maintained an illusory attitude of queenly beauty in spite of her distorted face and snagged teeth. Intrusion into her personal life was strongly resented.

At necropsy there was "a generalized visceral involvement limited to minute vessels. There was an exudative peri-vascular reaction, whose cellular character was difficult to classify. The kidneys, whose surfaces had a flea bitten appearance, the lungs and heart were severely involved."

Summary: The evolution of this vascular disturbance was complete in four years because a very rigid personality preferred death to acceptance of a life situation in which her husband rather than her paramour was to be her symbol of love and security.

Case 6. (1949.) A 25 year old female had worked as a stenographer until three years before. With the expansion of business more stenographers were hired and she was made their supervisor. Less than two months later she was no longer able to type because her fingers were cold and numb. They became discolored and rigid, and she had to give up her work. Alone, she went to Arizona seeking a cure in its hot sun. She found that she was no better there and returned home to her parents and a kind brother.

When seen in the clinic she showed evidence of severe scleroderma of the face and hands. There was no visceral involvement. Several injections of 25 mg. of Priscoline into a small brachial artery just above the elbow caused an intense erythema and warmth of the hands. This response encouraged the patient to believe that her hands could become warm again. After several discussions she accepted, on faith rather than insight, the relationship between the onset of her disturbance and the sudden thrust of responsibility on an admittedly dependent and unprepared person. As her fingers improved she was able to obtain a position with civil service security. The kindly personnel manager was willing to overlook her partial disability. The skin became more supple and the wounds healed. Her face lost some of its sclerous character.

Summary: Sudden advancement to a job with greater responsibility in the face of the patient's insecure personality and lack of ability brought about the severe vasospasm and scleroderma. Vasodilatation by drugs, some insight and a position to fit her stature have begun the reversal of the pathologic derangement. The obliterative changes will delay full recovery as much as the incomplete resolution of her basic personality fault.

Case 7. A 30 year old female (previously reported [8]) was first seen for Raynaud's in 1943, when it was felt that her disease was due to the constant state of terror in which her husband kept her: he would strike whenever she disagreed with him. She was able to understand and accept the psychosomatic relationship between her home life and her disability, but felt that she was unable to care for their child alone and therefore decided to live with him.

(1950.) The patient came to obtain a statement, needed for divorce proceedings, which would describe her vascular disease. During the previous year she had begun to work. Her child was now old enough to be left alone, and her salary was sufficient for both of them. Her husband was still not aware of what she contemplated. She thought it would be of interest to me to know that on the very day she signed the legal papers in her lawyer's office a great change had occurred in her illness. Her hands no longer turned blue, white and numb, and the skin felt much more supple. All this had happened despite the fact that she still lived under the same roof with her husband.

Summary: Ten years of vasospasm and progression to scleroderma have ended abruptly with the certain knowledge that she will soon begin a new life, secure and unmarred by an abusive husband.

Discussion

The primary physiologic disturbance in Raynaud's disease and scleroderma is an increase in the tonus of the precapillary sphincters. These are located at a point where the capillary buds off from the arteriovenous metarterioles. By this anatomic arrangement, when the capillary sphincter is completely closed circulating blood by-passes the capillary and is shunted through the arteriovenous anastomosis. We have previously shown that sympathetic nerves control arteriovenous blood flow, and that histamine may be the hormonal effector of the precapillary sphincter.[7]

Inspection through a skin microscope of the cutaneous capillaries of our patients with Raynaud's disease and scleroderma shows that blood flow is abnormal. Instead of being rapid, spurty and difficult to follow, it flows in a leisurely fashion, or intermittently, often giving the capillary a beaded appearance. The arterial limbs are narrow, threadlike; venous limbs are dilated, tortuous and lengthened. The spasm is cyclic in the mild case and sustained when the disturbance is severe. These microscopic aberrations mirror the objective physical changes. Short cycles of pallor and reactive hyperemia characterize the mild case, while the skin in the severe case remains permanently cold, numb and cyanotic. When the subcutaneous tissues become involved the sclerous phase of the disease develops. The arteriovenous anastomoses are narrowed by vasospasms or thrombosis. Few capillaries are visible. If venules are visible they are dilated, margins are fuzzy and flow is stagnant. Connective tissue disintegrates, elastic tissues disappear, and collagenous fibers increase in density and bind the skin to the deeper tissues, giving the skin a pitted and ironed-out appearance. When this process overlies the phalangeal joints they become constricted, losing their mobility. Sclerodactyly describes this state. When scleroderma involves the face it causes a masklike, pinched appearance, with furrows radiating from the corners of the mouth and eyes. The temperature of the sclerous and atrophic skin follows changes in environmental temperature in the manner of an inert body. Clinical studies of the viscera elicit little information before their functional decompensation is close at hand. Kidneys, heart, lungs and brain are most frequently involved. Microscopic examination at necropsy shows a nonspecific cellular reaction about the arterioles and capillaries, and an increase in interstitial connective tissue and collagen. The microscopic picture and its interpretation always varies with the pathologist of the hospital in which the patient died. Each emphasizes a different pathologic characteristic. This would indicate that tissue and vessel reactions to anoxemia when caused by vasospasm are nonspecific in character.

What is the etiology of this derangement, which can manifest itself as a localized cyclic vasospasm of digits, or as a generalized vasospasm, with its sequel, visceral scleroderma and death? The case reports demonstrate a consistent evolution of a psychosomatic pattern. Each patient had a commensalistic personality which made him susceptible to threats of death, in-

digence, or the loss of a significant protective love object upon whom the patient for a long time had been emotionally overdependent. The actual fulfillment of such a threat to security occurred in each case, and was promptly followed by the onset and persistence of the manifestations of vasospasm and its sequelae. The emotional triad characterizes all our cases of Raynaud's disease and scleroderma. The intensity and introversive character of the anxiety experienced by these patients are a striking feature of these clinical disturbances, though they may not be specific for these conditions. The personality deviation varied from a mild anxiety state to one of psychotic dread. Some physicians have sensed,[1, 2, 4, 8] while others have confirmed, with or without reservations, this direct relationship.[3, 9] It can easily be realized that the response to therapy will (and did, in our scleroderma group) depend upon the degree and rigidity of the patient's personality and the level of his intelligence. Contrary to the opinion of some, we found that the majority of these patients belong to the nonpsychotic group. They certainly are worthy of an attempt at reclamation by the understanding physician. Our case histories and psychologic examinations, such as the Rorschach, show that these patients have not attained this state of dread by accident. They were vulnerable at all times. The anxiety was one of expectancy. Man without experience cannot develop this. When he becomes aware of the possibility of a difference in the status of his own personal safety, he becomes pervaded by this sense of dread, which is expectant. It is now a factor of his personality and becomes a determinant of his behavior in situations in which his personal safety or well being is threatened. While the tenor of his life is unruffled he goes on with few or no symptoms. This state of relative quiet continues only until the patient experiences a severe threat to or an actual loss of personal safety. Expectation is now a reality, and a confirmation of his dormant dread. The ability of the patient to integrate this manner of personality into his routine of living is variable. The trigger mechanism which weakens and relaxes the control of this dormant and unstable personality is the sudden but persistent change in the life situation. Its full effect continues because the individual lacks the ability to absorb or ignore the shock to his equilibrium. The case reports demonstrate that all the patients with scleroderma were unable to do this before treatment. The full effect of failure was expended upon their sympathetic pathways and the minute vessels. The discomforts of the disease confirmed and further compounded their fears.

An opportunity to sense the quanta of vasospasm generated by fear presented itself in case 3. While this patient was receiving a test arterial infusion of a dilute solution of histamine [6] into her femoral artery her skin became a bright red from the groin to the tip of her toes, skin temperature rose six degrees on the dorsum of her foot, and the superficial veins distended. In the midst of the infusion several visitors (medical) entered the clinic. The history and its relationship to her disease were discussed in her presence.

During questioning by the visitors she related how she had been upset this week by the death of her father-in-law, who had always been kind to her. Suddenly, in spite of the continuing flow of histamine, her toes and half of her foot turned pallid parchment yellow, the skin cooled and the superficial veins collapsed. Noting this cause and effect the visitors walked out, leaving her without an audience. A few moments later her foot and toes became red and hot. The mere recital of a recent event involving death had reversed vasodilatation, even while the vasodilating infusion was flowing. By comparison, the forces expended on the autonomic nervous system by the psychologic imbalance present in patients with scleroderma must be enormous. This and the additive effect of chronicity must be the basis for the widespread destruction found clinically and at necropsy. Skin temperatures recorded during psychoanalytic interviews [9] fell little in the mildly frustrated but a great deal in the severely frustrated and chronically uncompensated patient. Those able to develop a safety escape device through an illusory sense of being masters of their life situation had no drop in skin temperature during their discussions. Since the onset of the scleroderma always coincided with the occurrence of emotional trauma, the existence of a psychosomatic bond has been clearly established. In Raynaud's disease [5] it was repeatedly shown that when this nexus was broken symptoms disappeared. In our patients with scleroderma a similar reversal and halt to the progression of the somatic manifestations followed a sustained improvement in their life situations. Only then could the sequelae based on the thrombotic disturbances become amenable to therapy. Failure to resolve their problems, either because they were insoluble or because our patients' integrative abilities were severely limited, resulted in a relentless progression of the disease, regardless of therapy, medical or surgical.

Support for this viewpoint is found in the recent observations made by Dr. James C. White during a discussion of a case presented at a clinicopathological exercise [10]: "From past experience I have become very allergic to this group of diseases because a number of times I, and other surgeons, have done sympathectomies on persons who appeared to have Raynaud's disease only to find that they progressed to scleroderma. Under these circumstances operation has either made the condition worse or produced no improvement. It is of interest in the hospital history, to note that, as she was talking about her Mongolian child, the patient became extremely upset and developed striking vasospastic changes." Dr. White's decision should be more generally shared.

Conclusion

Evidence collated from a clinical and psychologic study of several patients supports the belief that scleroderma, like Raynaud's disease, is a manifestation and the result of a psychosomatic disturbance with a definite pattern. The patient's sense of security always depends upon a commensalistic type

of existence. When by force of circumstances this is destroyed, the inflexible nature of his personality does not permit readjustment. The dread fear initiates a generalized spasm of the minute vessels and the evolution of cutaneous and visceral scleroderma. While this life situation is operative the process persists and is cumulative in its self-destruction. If and when security is reëstablished by chance or design, the process is reversed and the complicating thrombotic manifestations become amenable to vasodilating therapy. To attempt such therapy without first reëstablishing security is to court failure and disappointment which, in turn, aggravate the disease.

Though the problem was presented from the medical viewpoint of one interested in peripheral vascular disease, we required the coöperative help of the psychiatrist, the surgeon, the psychologist and the social worker to gain this insight, which frequently prevented the evolution of simple vasospasm to scleroderma.

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FATAL TRANSFUSION REACTIONS FROM CONTAMINATION OF STORED BLOOD BY COLD GROWING BACTERIA *

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The immense value of blood transfusion in anemia and in pathologic states associated with a depleted blood volume is well recognized. For the most effective use of blood, a supply must be immediately available. The natural outgrowth of the clinician's requirements has been the storage of blood in blood banks.

While the benefits of transfusion far outweigh the risk, there is a significant hazard in the administration of stored blood. The mortality from blood transfusion has been estimated to be as great as or greater than that from an appendectomy.[1] The three outstanding dangers are homologous serum hepatitis, reactions due to incompatible blood, and bacterial contamination. Few reports are available regarding the hazard of blood contamination.[2-6] Limited personal inquiries have disclosed seven unreported fatalities, as well as numerous nonfatal reactions due to administration of blood containing large numbers of bacteria. These data indicate that this complication of transfusion is a more frequent occurrence and a more serious problem than the literature would indicate.

The occasional contamination of stored blood is inevitable, since it is impossible completely to sterilize the skin through which the phlebotomy needle is inserted,[7] and since there is no effective method of sterilizing blood once drawn without damage to the blood. While earlier reports indicated more frequent contamination,[8, 9] an incidence of 1 to 3 per cent may be expected in modern blood banks.[6, 10-12] These studies are based on cultures of blood incubated at 37 or 32° C. Many organisms detected at these temperatures are either arrested or killed at the temperature of storage of blood (4 to 7° C.), and therefore rarely produce serious reactions. On the other hand, certain gram-negative bacilli do not grow at temperatures of 32° C. or above, but multiply freely at the storage temperature of blood. It is this group of organisms that have produced the most serious transfusion reactions. At present there are no adequate cultural studies to indicate the frequency of contamination of bank blood by these cold growing organisms. The contamination reaction, designated so appropriately by Whitby [3] as "transfusion catastrophe," represents a specific clinical syndrome

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which is well illustrated in the following report of a fatal reaction due to a cold growing organism.

Case Report

An 18 year old white male received approximately 250 ml. of packed red cells from a unit of blood drawn in acid-citrate-glucose preservative and stored for four weeks at 4° C. The clear plasma was removed and discarded immediately before transfusion. The transfusion was completed in one hour. Ten minutes before its termination the patient complained of headache, followed by nausea and an urge to urinate. Upon completion of the transfusion he walked to the bathroom, vomited and defecated, and returned to bed feeling better. Fifteen minutes later there occurred a severe shaking chill which lasted about 20 minutes, associated with mild low back pain and with a rise in temperature to 105° F. Within one half-hour of

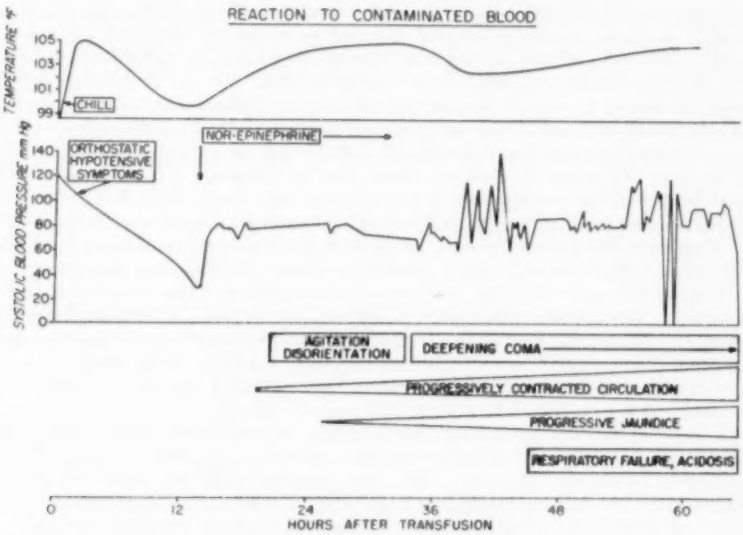

Fig. 1.

completion of the transfusion the patient noticed faintness and dizziness on sitting upright. Blood pressure, first measured four hours after the transfusion, was found to be 80/40 mm. of Hg.

During the first 12 hours the fever, nausea, back pain and headache abated, but hypotension and general weakness increased. Conjunctival vessels were intensely injected and the face appeared puffy, particularly about the eyes. Because of the presence of gram-negative bacilli observed in a smear of blood remaining in the transfusion bottle, terramycin and streptomycin were administered within six hours of the reaction.

By the twelfth hour after transfusion the systolic pressure had fallen, first slowly and then precipitously, to below 30 mm. Hg. Despite the hypotension, extremities were warm, the entire body was suffused, and peripheral pulses were easily palpable. The patient was well oriented but experienced great fatigue and became faint when his head was even slightly elevated. At this time an infusion of nor-epinephrine was

begun, and with this it was possible to maintain the systolic pressure at 60 to 90 mm. Hg during the following 12 hours. Intense vasoconstriction proximal to the needle at times limited the infusion rate. Elevation of systolic pressure above 120 mm. Hg was accompanied by diarrhea, retching and an agitated behavior. One thousand milliliters of whole blood were given during this time without demonstrable effect on the blood pressure.

On the second day the patient became agitated and disoriented, requiring restraint and sedation. Between 50 and 100 ml. of adrenal cortical extract and about 100 mg. of cortisone were given without improvement in the clinical picture. He became semicomatose, with occasional lucid intervals. A mucous, blood-tinged diarrhea and black vomitus were noted. His blood pressure could be regulated at any desired level by altering the infusion rate of nor-epinephrine, but without continuous infusion the systolic pressure fell to unobtainable levels. Peripheral vasoconstriction became progressively more severe over the 66 hour period. Extremities became cool and pale, while arterial pulsations first diminished and then disappeared in the extremities. Jaundice appeared during the second day and progressively deepened. Respirations became rapid and shallow and were not altered by oxygen or helium-oxygen inhalation. Urinary output was limited to a total of about 500 ml. of blood-tinged fluid during the second and third days, and the blood urea nitrogen rose to 80 mg. per cent. The pH of the arterial blood on the third day was 7.2 and decreased to pH 7.12 despite the intravenous administration of over 40 gm. of sodium bicarbonate. Blood clotting was prolonged to over one hour, but an adequate clot eventually formed. Blood volume (P32), determined a few hours before death, showed a red cell mass of 2,190 ml. and total volume of 4,670 ml., which corresponded to his predicted volume on a height-weight basis. Coma deepened and death was associated with jerky, ineffective respirations and with a marked reduction in cutaneous circulation.

*Autopsy Report:** Serosal surfaces of peritoneum and thorax were smooth and glistening. There were approximately 800 ml. of free bile-stained peritoneal fluid and about 100 ml. of fluid in each chest cavity. Retroperitoneal tissues appeared edematous. Petechial hemorrhages in moderate numbers were seen on exposed serous surfaces. The *heart* was of normal size with firm muscle, and except for a few petechial hemorrhages showed no gross or microscopic evidence of disease. The *lungs* weighed 380 and 450 gm. and were a deep red color but without edema, atelectasis or pneumonitis. In histologic section, marked congestion of red cells in the capillary network was observed. The *liver* weighed 1,670 gm. and was normal in appearance. The lobular architecture of the liver lobules was undisturbed, although individual liver cells showed mild swelling. The *spleen* weighed 330 gm. The parenchyma was firm and deep red on cut section. The *kidneys* weighed 200 and 190 gm. The cortices appeared slightly pale, while medullary areas were a deep red. The glomeruli were normal. The tubules not infrequently contained heme casts or red cells. Slight to moderate dilatation of tubules was seen, and lining endothelial cells often appeared flat. Occasional fragmentation of tubules was seen. Capillaries through the medullary area were dilated and filled with blood. The adrenals were not hemorrhagic. Rare zones of "lacunar" degeneration of cells in the zona glomerulosa with occasional necrosis were seen histologically, but for the most part the glands were quite normal in appearance. The stomach mucosa contained an ecchymotic area 7 by 8 cm. above the pylorus. The intestine was remarkable only for the sporadic petechiae; its mucosa was intact. No bacteria or focal abscesses were seen in any of the tissues.

Comment: The observed dilatation of the capillary bed, while unaccompanied by recognizable capillary damage, is consistent with the vasomotor

* We wish to express our appreciation to Dr. David G. Mason, who performed this autopsy and made all material available to us.

failure exhibited by the patient. The renal lesion is similar to changes ascribed by Oliver et al.[13] to cortical ischemia. Adrenal changes and those in other organs were minimal.

Special Studies of the Transfusion Reaction

During the transfusion reaction blood was drawn, centrifuged and examined for hemolysis; none was visible. Bloods from donor and recipient were retyped and crossmatched and were again found compatible. A smear of the remainder of the transfused blood showed numerous gram-negative rods. The patient's blood drawn three hours after the reaction and examined in similar fashion showed no organisms. A blood culture taken at this time became cloudy after three days of incubation at 37° C. and contained gram-negative rods. However, subcultures at 25° and 37° C. showed no growth. All subsequent cultures from the patient incubated at 24 and 37° C. were negative.

Cultures of the blood transfused resulted in the isolation of a gram-negative rod, classified as *Pseudomonas* sp. on the basis of the following characteristics:

Rods, 0.5 to 0.9 by 1.4 to 2.5 microns, occurring singly and in pairs with a few short chains. Motility by a single polar flagellum. Gram-negative. On nutrient agar the colonies were large, convex, moist and cream colored. On blood agar the colonies were white and nonhemolytic.

Gelatin slowly liquefied. Small amounts of acid with no gas formed from arabinose, glucose, levulose, maltose, sucrose, glycerin and mannite. No acid formed from galactose, xylose, lactose, salicin, inulin or dulcitol. Heavy pellicles formed on broth. Starch was not hydrolyzed. Litmus milk became alkaline in seven to nine days and slowly reduced after 11 days with slight peptonization. Urease not formed. Indole, methyl red and acetylmethylcarbinol tests were negative and citrate positive. No H_2S formed. Nitrates reduced to nitrites. Serum not liquefied. Aerobic. No pigment produced in 14 days.

Abundant growth obtained at temperatures from 4 to 29° C., inclusive, with scanty growth at 30° C. and none at higher temperatures.

This *Pseudomonas sp.* most closely resembles *Ps. geniculata* (Bergey, 6th Ed., 1948). It differs primarily in that it reduces nitrates and is not facultatively anaerobic.

Similar organisms were found in the refrigeration area where the blood had been stored, in centrifuge cups and on other laboratory surfaces. Since this blood had been entered on the day it was drawn it is assumed that, in spite of the precautions used, contamination occurred at this time. No hemolysis, abnormal pigment formation or odor was produced in the plasma of the infected blood.

The toxicity of the organism was demonstrated in animals. After culture on basal salts agar with 0.5 per cent glucose, organisms were injected intravenously into dogs and produced nausea, vomiting, hyperpyrexia, hypotension and death. These preliminary observations are being extended to determine the nature of the toxic substance.[14]

TABLE I

Summary of Clinical Experience with Reactions from Contaminated Blood

Case No.	Storage Days	Vol. Given, c.c.	Duration of Reaction	Outcome	Bacteriologic Studies on Donor Blood	Author's Name	Ref. No.
				A. Gram-Negative Organisms			
1	14	120	3 hrs.	Death	Gram-neg. rod (coliform bacilli) on smear and culture.	Whitby	15
2	15	25	9 hrs.	Death	Gram-neg. rods (Pseudomonas and coliform bacteria) on smear and culture.	Whitby	15
3	15	50	2 days	Recovery	Gram-neg. rods (Pseudomonas and coliform bacteria) on smear and culture.	Whitby	15
4	—	—	4 hrs.	Death	Gram-neg. rods (*B. coli aerogenoides*) on culture.	Whitby	15
5	—	—	4 hrs.	Death	Gram-neg. rods (*B. coli aerogenoides*) on culture.	Whitby	15
6	—	—	4 hrs.	Death	Gram-neg. rods (*B. coli aerogenoides*) on culture.	Whitby	15
7	—	—	4 hrs.	Death	Gram-neg. rods (*B. coli aerogenoides*) on culture.	Whitby	15
8	2	—	Minutes	Death	*B. coli*—heavy growth. Also strep. and anaerobic bacilli.	Officer	5
9	6	200	1 day	Death	No studies on these donor bloods.	Raygorodskiy	16
10	—	—	—	Death	All were from one batch of bloods, drawn same day, and most of the remaining bottles were contaminated with "gram-neg. rods and spore-formers."	Raygorodskiy	16
11	—	—	—	Death		Raygorodskiy	16
12	—	—	—	Death		Raygorodskiy	16
13	—	—	—	Death		Raygorodskiy	16
14	5	250	Several days	Recovery		Raygorodskiy	16
15	—	200	Several hours	Death	Gram-neg. rods cultured from patient's blood and spleen. Donor blood not examined.		
16	28	250	66 hrs.	Death	*Pseudomonas* sp. (case reported this article)		
17	17	75	5 days	Recovery	Pseudomonas on culture.		18
18	13	250	3 days	Death	Pseudomonas on culture.		18
19	11	50	—	Unknown	Pseudomonas on smear and culture.		18
20	—	—	2 hrs.	Death	*P. aerogenoides* on culture.		18
21	—	—	10 days	Death	*P. aerogenoides* on culture (Bact. endocarditis).		18

TABLE I—*Continued*

Case No.	Storage Days	Vol. Given, c.c.	Duration of Reaction	Outcome	Bacteriologic Studies on Donor Blood	Author's Name	Ref. No.
22	—	—	2 days	Recovery	Gram-neg. rods on smear. No culture.		18
23	—	—	1 day	Recovery	Gram-neg. rod and diphtheroid on culture.		18
24	13	375	4 days	Recovery	Gram-neg. rod and hemol. *Staph. aureus* on culture.		18
25	18	375	6½ days	Death	Gram-neg. rod (achromobacter) on smear and culture.	Borden	2
26	12	500	2½ days	Death	Gram-neg. rod (*Paracolobactrum aerogenoides*) on smear and culture.	Borden	2
27	35	140	1 day	Recovery	Gram-neg. rod on smear. Culture at 37°C. neg.	Strumia	19
28	—	100	—	Death	*Alcaligenes faecalis.*		18
29	—	100	—	Recovery	Gram-neg. and + bacilli with spores.		18
30	—	500	—	Recovery	Gram-neg. bacillus.		18
31	—	—	—	Recovery	*Alcaligenes faecalis.*		18
32	—	50	—	Recovery	Gram-neg. bacillus.		18
					B. Organisms Not Known		
33	13	30	1 day	Recovery	Not done.		18
34	17	150	3 days	Recovery	Negative smear and culture.		18
35	18	400	2 days	Recovery	Negative smear and culture.		18
36	—	200	1 day	Death	Not done.		18
37	—	40	12 hrs.	Death	Many organisms on smear. Not identified.	Mollison	4
38	—	100	10 days	Death	Rod not identified.		18
					C. Gram-Positive Organisms		
39	15	—	5 days	Recovery	Corynebacterium on smear and culture.		18
40	—	200	1 day	Death	*Staph. aureus* on smear and culture.		18
41	1	75	10 hrs.	Recovery	Diphtheroids on smear and culture.	Braude	6

Summary of Reactions Following Bacterial Contamination of Stored Blood

In table 1 are summarized the pertinent data from published reports, from case records reviewed by us and from material kindly supplied by others who have observed such cases.

The clinical manifestations appear to vary chiefly in intensity and may be abbreviated as follows:

1. A prodromal period of less than an hour, including a feeling of fullness in the head, headache, restlessness and chilly sensations (0 to 30 minutes).
2. Violent chill lasting 10 to 30 minutes, with a precipitous rise in temperature (30 to 60 minutes).
3. Flush phase associated with extreme vasodilatation, seen best in the conjunctivae, warm skin, abdominal discomfort with some nausea, vomiting and diarrhea, and falling blood pressure (onset, one hour).
4. Shock phase, with loss of vasomotor regulation, marked orthostatic hypotension, but with persistent hyperemia of the skin (onset, one to six hours).

It should be emphasized that initial symptoms (1) and (2) and, to some extent, (3) are not specific and may be indistinguishable from a hemolytic or "pyrogenic" reaction. The onset of severe hypotension with warm extremities (red shock) is the characteristic feature of "transfusion catastrophe" due to bacterial contamination. Death has occurred with administration of as little as 25 ml. of blood and in as short a time as three hours. In this series of cases there is a mortality of over 50 per cent, and of 65 per cent in those instances attributable to gram-negative organisms. This is not considered to reflect the true incidence of contamination reactions, since mild febrile episodes are usually assumed to be "nonspecific" pyrogenic reactions.

Organisms isolated from transfusion reactions are capable of growth at a wide temperature range. The growth characteristics of 14 such organisms, collected from various parts of the United States, are listed in table 2. Eight of the 14, all strains of pseudomonas, grew well at refrigerator temperatures but did not multiply at 37° C. Ten of the 14 organisms showed good growth even at subzero temperatures, as has been described for other cold growing organisms.[20] It is of interest that all 14 organisms were sensitive to terramycin and aureomycin. Bacteriologic characteristics of cold growing organisms contaminating blood have been recently described by Pittman.[21]

Discussion

Reactions following administration of contaminated blood, plasma or parenteral fluids vary greatly, depending on the type and number of microorganisms. There may be no detectable reaction, or there may be a febrile

response or the onset of profound shock characteristic of the severe reaction. The usual airborne contaminants, such as micrococci and diphtheroids, though present in large numbers, may produce little reaction.[6] As shown in table 1, gram-negative bacilli, especially members of the coli-aerogenes group and pseudomonads, produce severe and frequently fatal reactions.

The evidence presented indicates that microörganisms capable of growing at low temperatures are responsible for the more serious reactions. The low temperature at which blood is stored permits growth of these organisms, whereas the usual bacterial pathogens are restrained. This problem is similar to that encountered in the frozen food industry and by marine bacteriologists.[22, 23] Cold growing organisms are abundant in nature and may be frequent contaminants in the laboratory, *particularly in refrigerated areas.*

TABLE II

Temperature Requirements and Antibiotic Sensitivities of Gram-Negative Bacilli Contaminating Stored Blood

No.	Organism	Temperature °C.			Inhibiting Concentration of Antibiotic (Micrograms per ml.)				
		37° C.	2–6° C.	minus 2° C.	Aureomycin	Terramycin	Chloramphenicol	Streptomycin	Polymyxin B
1	*Escherichia intermedium*	+	−	−	<5	< 5	50	50	< 1
2	*Escherichia intermedium*	+	−	−	<5	< 5	50	50	< 1
3	*Paracolobactrum* sp.	+	−	−	<5	< 5	10	50	>50
4	*Paracolobactrum* sp.	+	+	−	<5	< 5	50	10	>50
5	*Flavobacterium* sp.	+	+	+	<5	< 5	< 5	10	50
6	*Flavobacterium* sp.	+	+	+	<5	10	10	>50	>50
7	*Pseudomonas* sp.	−	+	+	<5	< 5	50	50	< 1
8	*Pseudomonas* sp.	−	+	+	<5	< 5	50	>50	< 1
9	*Pseudomonas* sp.	−	+	+	<5	10	10	>50	>50
10	*Pseudomonas* sp.	−	+	+	<5	< 5	< 5	>50	>50
11	*Pseudomonas* sp.	−	+	+	<5	< 5	>50	>50	>50
12	*Pseudomonas* sp.	−	+	+	<5	10	>50	>50	>50
13	*Pseudomonas* sp.	−	+	+	<5	< 5	50	>50	>50
14	*Pseudomonas* sp.	−	+	+	<5	10	>50	>50	>50

"Cryophile" bacteria were reported in 1947 by Edsall and Wetterlow [24] as contaminants of plasma and were observed to be pyrogenic. The same year there was reported contamination of streptomycin solutions by similar organisms which did not grow at 37° C.[25] The importance of these organisms is obvious from the present case and from the experience of others, summarized in table 1.

These bacteriologic considerations apply equally to plasma transfusions. Instances of contamination from a variety of organisms have been reported,[26–28] and fatalities have occurred from the same cold growing bacilli described in this paper.[18]

The toxicity of these organisms would seem to be unrelated to their invasiveness, since the reaction appears abruptly and since many of the bacteria are incapable of multiplication at body temperature. Thus it may

be assumed that the organism contains or produces a toxin responsible for the reaction. A general correlation exists between this toxicity and the pyrogenic capacity of organisms. Thus, the gram-negative organisms which produce the fulminating reactions are about 100 times more pyrogenic than gram-positive bacteria.[29]

While pyrogenic substances isolated from these gram-negative rods are capable of producing chills, fever and hypotension,[30] it is not at all clear whether the fever-producing and shock-producing factors are the same.[31, 32] In the dog, large amounts of Piromen, a pyrogenic substance obtained from a pseudomonad, did not produce the same hypotensive and lethal reaction as was observed following injection of the organism responsible for the fatality reported here.[14]

The shock encountered with this organism resembles that found in septicemia due to gram-negative bacteria,[35] and the nonspecific pathologic changes are similar to those reported in experimental studies of bacterial toxins. There was no blood volume change in the case reported to account for the shock, and blood transfusions were without effect. Since endotoxins of gram-negative bacteria have been shown to damage vascular endothelium,[33] it seems likely that such local injury with loss of vasomotor activity was responsible for the shock.

At the present time it is impossible to state the incidence of contamination of blood and blood products by cold growing organisms, because of the inadequacy of cultural studies at temperatures below 32° C. In one institution during the past year all bloods have been screened by examining a stained smear before transfusion.[34] Out of 3,000 bloods examined, six were found to contain organisms at an average storage period of six days. In all six instances the organisms were gram-negative rods and the bloods all appeared to be sterile on culture at 37° C.

The introduction of organisms must occur either through (1) inadequate initial sterilization of the bleeding equipment, (2) contamination of the skin surface through which the needle is introduced, (3) ingress of air and airborne organisms into the bottle during the phlebotomy procedure, or (4) entry into the bottle during the period of storage before transfusion. Adequate sterilization and the use of a vacuum bleeding bottle, with clamping off of the inlet tube before withdrawing the needle from the donor's arm, remove two of these possibilities.[1, 3] In the standard procedure of blood banking it is desirable not to enter the bottle before transfusion.[4] In some institutions blood is prefiltered to remove particulate matter capable of clogging the recipient set before its administration to the patient. This involves entering the bottle and must be considered an undesirable practice because of the possible delay between this procedure and the actual administration of the blood. The most difficult problem is the sterilization of the donor's arm. Numerous organisms may be cultured from the alcohol or Zephiran solutions used to prepare the skin surface. It would seem desirable

after cleansing with soap to apply tincture of iodine to the skin, waiting one minute before inserting the needle. The iodine should be removed by washing with alcohol after the phlebotomy is completed.

Despite rigid precautions it is likely that an occasional contamination of blood will occur. Since there may be no hemolysis or other gross evidence of the presence of bacteria, it is suggested that the *examination of a stained smear of every blood should be made immediately preceding its administration.* While various antibacterial substances incorporated in the preservative medium have been suggested,[36, 37] only the antibiotics appear promising. Their possible value has yet to be proved, and will in no way vitiate the importance of aseptic technic in drawing and handling of blood and blood products. All of the 14 gram-negative organisms tested in the present study were inhibited by relatively low concentrations of aureomycin and terramycin (table 2). The feasibility of adding one of these agents (probably terramycin, because of its greater stability) to transfusion bottles is under investigation.

Treatment does not appear to be effective, once serious reaction has occurred. Pressor substances such as nor-epinephrine may be helpful, and appeared life-saving in one instance of contamination of a saline-dextrose solution.[38] It was effective in maintaining blood pressure in the case reported here. The rapid disappearance of bacteria in this case and of pyrogenic substances from the blood stream in experimental studies would make exchange transfusion appear useless.

Summary

A fatal transfusion reaction due to contamination of stored blood by a cold growing organism, *Pseudomonas* sp., is reported. Forty other instances of bacterial contamination, only 20 of which have been previously described, are summarized and indicate the scope of this hazard.

The gram-negative, cold growing organisms responsible for the majority of severe transfusion reactions may not be detected by culture at 32° or 37° C. The clinical picture is that of profound shock, associated with cutaneous hyperemia. The recognition and prevention of bacterial contamination of stored blood are discussed.

Acknowledgment

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THE SYNDROME OF COUGH SYNCOPE *

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Described largely in foreign writings and reported under a variety of names † in obscure journals, the clinical entity of cough syncope is not well known to American physicians. Recent cardiodynamic studies of the syndrome by McCann and colleagues [1] stimulated interest, but there is in the American literature no full description of the clinical picture. From personal observation of 25 examples of the condition a distinct clinical syndrome has crystallized.

Historical Aspects

Although certainly known to Heberden [2] and possibly to Sydenham,[3] syncope following cough was first clearly described by Charcot [4] in 1876. Much information is found in the French literature, particularly in doctoral theses of a half-century ago.[5] Early articles appeared in Italian,[6] British [7] and American [8] literature, but until recently mention of it in the English language was confined almost solely to textbooks of otolaryngology. An exception is the recent admirable treatise of Baker's from Guy's Hospital.[9]

Terminology and Definition

The unfortunate choice of the term "laryngeal vertigo" by Charcot has been commented upon by many writers. In later communications [10] Charcot abandoned this term, but it persisted despite his objections. Of the many terms the most appropriate are Tussigenic syncope (Lian),[11] Post-tussive syncope (Flindt),[12] Tussive Syncope (McCann), and Cough syndrome (Baker).[9] The modification of Baker's term to Cough Syncope seems preferable.

The entity, a syndrome, not a disease, is directly defined as loss of consciousness preceded by coughing.

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† Laryngeal vertigo, vertige laryngé, laryngeal ictus, ictus laryngé, laryngeal epilepsy, laryngeal apoplexy, chorea laryngis, lipothymia laryngea, lipothynise laryngée, laryngeal syncope, Kehlkopfschwindel, Larynxcrisis, spasmus glottidis adultorum, complete glottis spasm in adults, a rare form of laryngeal neurosis, ictus primitif, ictus idiopathique, ictus essentiel, tussigenic syncope, ictus secondaire, ictus symptomatique, laryngoplegie, bronchial syncope, Larynxschwindel, la toux obnubilante, accident laryngé, la toux vertigineuse, laryngisme de l'adulte, apoplektiforme Bewusstseinsverluste bei kramphaften Husten, Halsneurose, spasme apoplectiforme du larynx, laringismo inhibitorio, the cough syndrome, tussive syncope, post-tussive syncope, tussigenic ictus, bronchial ictus.

Clinical Picture

Garel and Collet's description [13] in 1894 and Baker's in 1949 are unsurpassed. The main clinical features of our personal cases and 15 additional examples made available to us through the courtesy of colleagues are listed in table 1. The clinical episode and its terrain are poignantly summarized by the light touch of the cartoonist in figure 1.

Commonest in middle aged males, the patients are pyknic and slightly obese, of an outgoing personality, and frequently overindulge in tobacco, alcohol and food. Many of them are salesmen, food or liquor dealers. Four

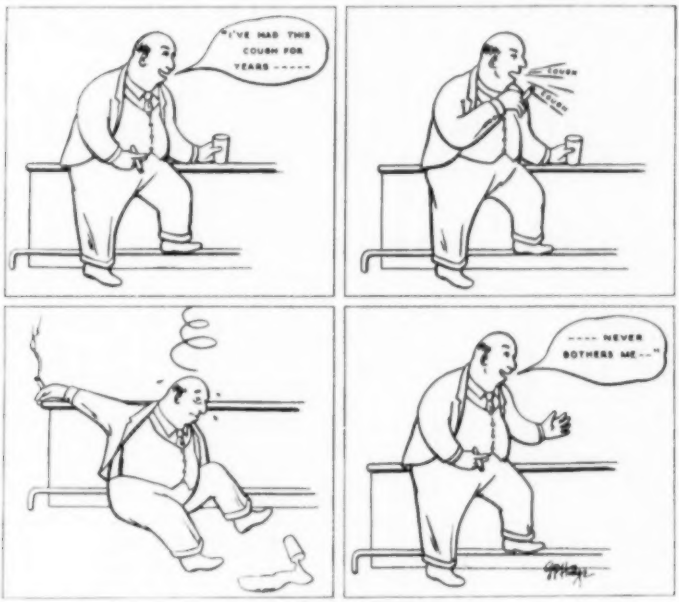

Fig. 1. Clinical features of cough syncope in pictorial sequence.

of our patients and 5 per cent of the recorded cases were physicians. They have frequent infections of the respiratory tract and often pulmonary emphysema or bronchial asthma. The syncope is sudden, and is noteworthy for its occurrence in any position. Recovery of consciousness is rapid and sequelae are minimal.

The average age of onset of the syndrome in our group was 47 years (figure 2). Of 290 reported patients, 97 per cent were males, and none of our cases occurred in women. Five of our examples were in Negroes. Only two of our patients were thin; the others were robust, strong, large chested and slightly obese. Several distributed more than 200 pounds over

TABLE I

Summary of 40 Cases of Cough Syncope

Case	Age at Onset	Sex	Color	Occupation	Duration of Syndrome	No. of Attacks	Convulsions	Injury to Self	Cigarettes	Alcohol	Physique	Comments
1. F. G. B.	60	M	W	Sea captain	6 mo.	30–40	No	No	1–2 packs daily	Liberal use	Very short, stocky and plethoric	Severe congestive heart failure due to pulmonary arteriolar sclerosis. Death during cough syncope.
2. A. T. B.	41	M	W	Jobber	2 yrs.	10–20	No	No	1 pack daily	Moderate	Athletic	Lobectomy for bronchiectasis cured cough syncope.
3. C. E. B.	47	M	W	Civil engineer	6 wks.	5–10	No	No	2 packs daily	Moderate	Moderate obesity, short stature	Bronchial asthma and obstructive emphysema.
4. J. B.	57	M	W	Designer	4 yrs.	5–10	No	No	Not available	Not available	Strong man	Attacks with recurring respiratory tract infections.
5. O. B.	41	M	C	Janitor		1	No	No	1 pack daily	None used	Normal build	Single episode of cough syncope 8 years ago—beryllium pneumonoconiosis.
6. R. B.	25	M	W	Physician	3 yrs.	5	No	Yes	1 pack daily	Moderate	Short and stocky	Attacks occur with bronchial asthma.
7. W. P. B.	56	M	W	Physician	8 yrs.	2	No	No	1–2 packs daily	Moderate	Strongly built, ruddy complexion	Two attacks 8 years apart—chronic bronchiectasis.
8. Dr. B.	58	M	W	Physician	22 yrs.	50–100	No	No	Excessively	Not available	Large, stout, ruddy	Died during paroxysms of cough syncope. Bronchiectasis.
9. A. C.	42	M	W	Business executive	2 mo.	4	No	No	Excessively	Rather heavy use	Obesity	Chronic laryngitis.
10. B. H. C.	47	M	W	Physician	10 yrs.	3	No	No	1½ packs daily	Moderate	Robust and red faced	Three attacks over 10 year period.
11. D. L. C.	55	M	W	Salesman	5 yrs.	10–20	No	Yes	1½ packs daily	Denied	Obese and barrel chested	—
12. J. W. C.	50	M	W	—	9 yrs.	500–1000	No	Yes	Heavily	Denied	Obese and robust	Hundreds of attacks over 9 year period.
13. M. R. C.	47	M	W	Oilfield worker		1	Yes	No	2 packs daily	Liberal	Very stocky	Diagnosed as myocardial infarction.
14. H. D.	50	M	W	Priest	1 wk.	10–12	No	No	Heavy smoker	Moderate	Large, florid complexion	Series of attacks accompanying lobar pneumonia 10 years previously.
15. A. I. E.	53	M	W	Salesman		1	No	Yes	4–5 cigars daily	Moderate	Obese	Solitary attack 7 years ago. None after weight reduction.
16. F. F.	40	M	W	Lawyer	5 yrs.	2	No	No	2 packs daily	Liberal	Well developed	—
17. T. L. F.	38	M	W	—		1	Yes	Yes	2 packs daily	Moderate	Obese, red faced	Solitary attack in patient not seen again.
18. J. H.	54	M	W	Jeweler	6 yrs.	5	No	No	1 pack daily	Moderate	Well built	—
19. A. J.	38	M	C	Laborer	1 yr.	15	No	Yes	1½ packs daily	Moderate	Obese	Sat on floor to minimize injury-sarcoid.

TABLE I—*Continued*

Case	Age at Onset	Sex	Color	Occupation	Duration of Syndrome	No. of Attacks	Convulsions	Injury to Self	Cigarettes	Alcohol	Physique	Comments
20. T. F. J.	39	M	W	Construction foreman	14 yrs.	10–20	No	No	1–2 packs daily	Heavy	Obese and strong	—
21. H. L. K.	42	M	W	—	1 yr.	2	No	No	1½ packs daily	Moderate	Strong and vigorous	—
22. E. McL.	51	M	W	Automobile salesman	2 yrs.	Several	No	Yes	Excessively	Heavy	Robust	—
23. G. M.	37	M	W	Tavern owner	8 mo.	3	No	No	3 packs daily	Heavy	Strong, vigorous	Used voice to excess to quell boisterous customers in barroom.
24. M. W. M.	55	M	W	—	1–2 yrs.	Several	Yes	No	Chain smoker	Moderate	Short and well built	Confused with epilepsy.
25. C. R. N.	30	M	W	Truck driver	3 mo.	Several	No	No	Moderately	Moderate	Strong, heavy set	Abnormal EEG with "response" to Mesantoin.
26. R. P.	54	M	C	Tavern owner	7 yrs.	12	No	Yes	2–3 packs daily	Moderate	Large build	Attacks occurred after cerebrovascular accidents.
27. D. A. R.	60	M	W	Tavern owner	1 mo.	Several	No	Yes	Not available	Not available	Short, powerfully built	Arteriosclerotic heart disease and emphysema.
28. G. D. R.	57	M	W	Attorney		1	No	Yes	Heavy	Heavy	Slightly built, thin	Hospitalized for questioned myocardial infarction.
29. J. R.	55	M	W	Mill superintendent	1 yr.	Several	No	No	1 pack daily	Moderate	Strong, large chested	Patient laughed at attacks, which frightened his wife.
30. E. A. S.	47	M	W	Carpenter	3 mo.	10–12	No	Yes	1½ packs daily	Moderate	Strong, slightly obese	See illustrative case report.
31. J. W. T.	43	M	W	Crane operator	8 yrs.	15–20	No	Yes	2 packs daily	Not available	Obese, heavily built	Recurrence of attacks after 8 year period of freedom. Most attacks occurred while lying in bed.
32. N. V.	30	M	C	Brickyard worker		1	No	No	Not available	Not available	Tall and thin	Single attack 7 years prior to death from silicosis.
33. A. J. W.	42	M	W	—	2 yrs.	4	No	Yes	Not available	Not available	Stocky, ruddy complexion	Attack while driving car caused injury to himself.
34. A. M. W.	47	M	W	Salesman	3 yrs.	Dozens	No	Yes	Excessively	Excessive	Obese, large man	Seemed to respond to symptomatic therapy.
35. N. K. W.	40	M	W	Welder	6 yrs.	2	No	No	Not available	Not available	Stocky, well built man	—
36. T. K. B.	52	M	W	Salesman		1	No	No	Heavy	Heavy	Heavy build	Considered as having heart attack.
37. H. T. E.	48	M	W	—		1	No	No	1 pack daily	Social	Stocky	Seen within past 2 months.
38. E. T.	33	M	C	Laborer	2 yrs.	7	No	No	2 packs daily	Moderate	Big and strong	Abandoned driving auto for fear of injury.
39. J. A. G.	35	M	W	—	10 yrs.	15–20	No	No	1–2 packs daily	Much	Obese and florid	—
40. M. A. C.	65	M	W	Oilfield worker	4 mo.	Several	No	No	Occasional	Denied	Strong and stocky	—

less than 5 feet 8 inches of height. Specific inquiry regarding smoking was answered in the affirmative by 35 patients questioned. Most classified themselves as heavy smokers. Alcohol was used by all but four of the 33 men asked. In many it was used liberally but in none was addiction present.

The pulmonary diseases associated with cough syncope in 30 of our 40 patients are listed in table 2. Chronic emphysema or bronchial asthma is usually present. As a complication of the latter, syncope after cough occurs in about 8 per cent of adult patients.[14] As a feature of pertussis in adults the syndrome was noted by Heberden.

The cough is dry, unproductive in nature, often a cascading paroxysm accompanied by extremely vigorous muscular efforts. At times only one sharp bark precedes syncope. Burning or tingling in the laryngeal region is described by some at the onset of cough.

The phrase "blackout" is frequently used by patients in describing the syncope. Use of this phrase has been helpful in eliciting the clinical history.

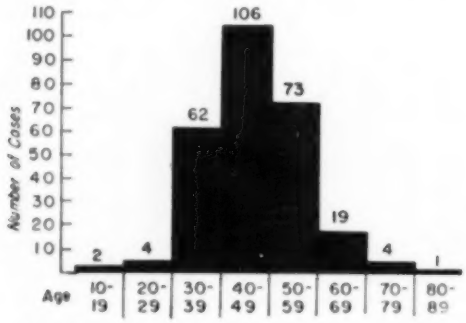

FIG. 2. Distribution of cases of cough syncope by ages at onset.

For each attack in which consciousness is lost there may be many minor episodes of giddiness and diminished vision. Usually after a few coughs there is no desire to breathe, a little giddiness and dimness of vision, and suddenly consciousness is lost. Muscle relaxation is complete. If standing, the patient falls; if sitting, he slumps in his chair; if lying down, his head rolls back. The face is turgid and congested, later to become pale. Diaphoresis often ensues. Convulsions, which occur in less than 10 per cent, are clonic in type and often limited. The duration of the attack is brief, often only a few seconds. Frequently the patient arises and blithely resumes his activity or conversation, being able to recall only having coughed. The attack is generally regarded as of little consequence, a factor accounting for the apparent low incidence of the syndrome. In many instances the sensation is described as pleasant. Contrasted with certain other types of syncope, more than half of the attacks occur in the lying or sitting position. A favorite setting is during or immediately after a heavy meal. A little warn-

ing, sufficient to prevent serious injury, is experienced by some. A still smaller number feel able to abort an attack by holding the breath, or firmly grasping an object for support.

The number of attacks is exceedingly variable. Some have but one attack, others have as many as 20 to 30 per day. The attacks vary with the course of the underlying respiratory disease, and when this is self-limited or remediable they disappear with its passing. With recurrent chronic diseases many attacks occur over several decades. Our case 12 had 500 to 1,000 attacks in a nine year period.

Although the attacks are generally stated to be benign, we have witnessed one death in an attack. Another reliable instance has been reported to us,

TABLE II

Associated Pulmonary Diseases in 40 Instances of Cough Syncope

Disease	No. of Instances
Emphysema	12
Asthma	10
Bronchiectasis	3
Pneumonoconiosis	2
Sarcoidosis	1
Pneumonia (acute)	1
Bronchitis (acute)	1
Total	30

and two other clear examples have been recorded.[15] These were in patients with serious cardiovascular disease.

An illustrative case report follows:

CASE REPORT

A 47 year old male carpenter of French extraction, jovial disposition and strong body build first fainted two and a half years ago after coughing while "strangulating" on a crumb of corn bread. Although cough (attributed by the patient to cigarette smoking) had been present for many years, this was his first episode of syncope. Consciousness was lost perhaps a dozen times. Three episodes occurred while he was lying in bed. During the last attack, one month ago, he cut his forehead in falling. His wife had witnessed most of the attacks, during which no convulsions were seen. Due to her consternation she was unable to estimate the duration of unconsciousness, but believed it was brief. The patient stated that on recovery he felt no ill effects and no mental clouding. There had been no fainting or syncope without the preceding cough.

The unproductive cough followed a tickle felt in the laryngeal region. For every major spell in which consciousness was lost, there were about a half dozen spells in which ringing in the ears and giddiness occurred. Syncope was preceded by bouts of severe coughing; light coughing produced no symptoms. The patient usually found that if he could grasp something he could prevent syncope. Only the initial attack occurred during eating. The syncope could not be induced voluntarily.

There was no family history of epilepsy. The patient had used alcohol in moderation. He had been a heavy smoker for 25 years.

Pertinent observations were: The patient was a large framed, well built, barrel chested, muscular middle aged man. There was moderate obesity in the abdominal

region. With full expiration, wheezes could be heard throughout the chest. Blood pressure in the sitting position was 140/92 mm. of Hg in the right arm; pulse was 88.

Hyperventilation, carotid sinus pressure and a blood pressure cuff wrapped about the neck inflated to 60 mm. of mercury for one minute failed to produce significant cardiovascular changes. The Weber maneuver produced a drop in blood pressure to 80/70 mm. of Hg and a sensation of giddiness.

Routine laboratory data, fluoroscopic examination of the heart and lungs, and vital capacity measurements were normal.

Reassurance was given. Since the patient had warnings before attacks, it was not felt necessary to interdict driving an automobile. He was asked to (1) stop smoking; (2) lose weight; (3) use analgesic throat lozenges, and bronchodilators. On six weeks of this regimen his cough lessened and he had no further attacks.

Diagnosis

Differential diagnosis is relatively easy. Always preceded by cough, the entity is distinguished from other types of syncope. A rare condition—the laryngeal crises of tabes dorsalis [16]—may imitate the cough syndrome in each detail. If no other stigmata of syphilis occur diagnosis must be inferential.

Several writers [17] have considered the condition to be intimately related to epilepsy. Unquestionably, some instances occur in which the cough syndrome seems to be an epileptic equivalent. In the main, however, the greatest number of individuals with the cough syndrome have not had stigmata of epilepsy. The hereditary and personal antecedents of the majority of individuals have revealed nothing that would relate to epilepsy. Most cases of epilepsy develop before the age of 25, and a large percentage appear before the age of six years, or before puberty.[18] Patients with tussigenic syncope have, in the main, had their first seizure at 45 to 50 years. Electroencephalograms have been recorded from eight patients, one of which was consistent with epilepsy.[17e] The relation with epilepsy seems to be similar to that of tabes, that is, there are certain few cases in which tussive syncope may appear with tabes [19] or epilepsy,[17] but in the very largest percentage of individuals there is evidence for neither.

There are certain points of resemblance with narcolepsy-cataplexy (Gélineau's syndrome [20]). An associated condition which is seen in patients subject to narcolepsy is a weakness of the muscular apparatus, usually of the legs, coming on suddenly while the patient is in the midst of some emotional display, usually laughter, and accompanied by the retention of consciousness.[21] This is given the name cataplexy. Cataplexy is characterized essentially by general inhibition of muscular tonus. Wilson [22] considers cough syncope intimately related to cataplexy on the basis of the sudden fall of the patient to the ground, the brevity of the attack, and the immediate and complete recovery. Against this is the observation of Levin [23] that cataplexy without narcolepsy is rare. In none of the cases of after-cough fainting has narcolepsy been mentioned. In addition, the loss of consciousness in the

cough syncope is complete. The age at onset differs in post-tussive syncope from Gélineau's syndrome in the same fashion that that of epilepsy differs from the cough syndrome. The course of the two conditions is quite different, for in the vast majority of cases of Gélineau's syndrome the symptoms are more or less stationary, and in only one of Levin's series did the symptoms disappear for any length of time.

The syncope was rarely properly diagnosed in patients seen by us. In four instances a verdict of coronary artery disease had been given. The physique, personality and pattern of chronic respiratory disease of these patients alert one to the proper diagnosis.

Pathologic Physiology

During coughing, exceedingly high pressures have been recorded from the intrapleural space, the superior vena cava, the right auricle, the right

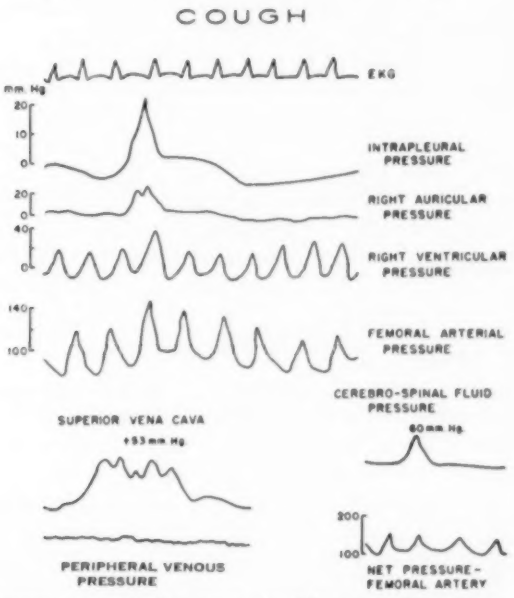

Fig. 3. Changes accompanying cough (modified from Hamilton,[24] Lauson [25] and McCann [1] and their co-workers).

ventricle, the pulmonary "capillary," the cerebral spinal fluid and the peripheral arteries [1, 24, 25, 26] (figure 3). Net changes in pressure, or changes in the gradient of flow from one area of the circulatory system to another, may be altered but little. In the pulmonary circuit, however, marked increase in the pulmonary artery pressure beyond that found in the pulmonary "capillary" is demonstrated in figure 4. McCann's patient was able to de-

velop high pressures in the right ventricle despite the presence of a bronchoscope which prevented closure of his glottis. During coughing, syncopal patients studied by Lian [11] and by McCann [1] displayed a sudden drop in peripheral arterial pressures. Syncope, however, was not reproduced. A similar drop with syncope was noted by Wilkens and Friedland [26] and McCann in cough syncope patients who fainted during the Valsalva (Weber) maneuver. Reflex bradycardia was not present.

The act of coughing has certain phases analogous to the Valsalva and to the Müller experiments. It is, however, more complex than these; and as Di Rienzo [27] and McCann have shown, high intrathoracic pressures can be achieved without closure of the glottis.

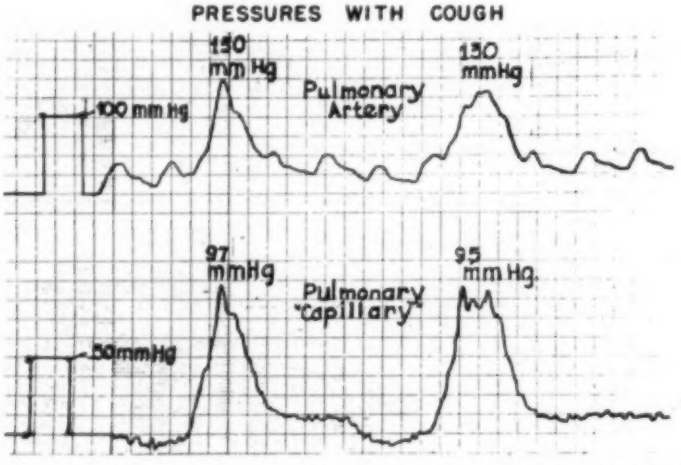

FIG. 4. Simultaneous measurements of pressures in the pulmonary artery and pulmonary "capillary" during two voluntary coughs in cough syncope patient N. V. (courtesy of Dr. Albert L. Hyman).

MECHANISM OF THE ATTACK

The definite mechanism of the syncope remains unproved. If it were certain in McCann's and our studies that right ventricular output did not increase during cough, then one would be confident pulmonary vasospasm was present. Animal experiments have indicated a reflex fall in peripheral arterial pressure with increased pressures in the pulmonary circuit and right side of the heart.[28] The analogy to the situation in cough syncope is not exact, and it remains to be demonstrated that the reflex is a potent one. Measurements of arterial oxygen saturation during coughing [1] and the Valsalva experiment [29] imply that anoxia—a demonstrated cause of pulmonary vasospasm [30]—is probably not present. Although certain clear examples of active vagus reflexes in cough syncope have been recorded,[31] the proper criteria of Engel [32] have not been applied in these instances.

The potentiating effect of previous hyperventilation in producing syncope with high intrathoracic pressure may play a minor part in those patients who faint after a paroxysm of coughing.[33] Any theory to account for the mechanism of syncope must, however, apply to those patients who collapse after one sharp cough. An inhibition of the reticular areas of the midbrain [34] may occur in these patients, but proof of this is lacking.

The failure of patients voluntarily to reproduce the syncope (in only nine instances has this been successful) has greatly hindered its investigation, and we must humbly agree to its appellation as a "will-o'-wisp" [35] while awaiting further opportunities and new investigative technics.

Clinical Picture Related to the Pathophysiology

There are certain features of the "terrain" of the clinical picture which summate to enhance syncope. In middle aged obese males the musculature of the thorax is capable of developing intrathoracic pressures higher than intra-abdominal pressures.[36] With loss of elasticity of pulmonary parenchyma in emphysema, intrathoracic pressures are not evenly transmitted,[37] and the dynamic vascular adjustments of these patients to stress are altered.[38] The reaction of pulmonary vasospasm to increased pressures in the thorax may be increased by excess smoking.[1, 39] The predilection for attacks to occur during eating, drinking or laughing would seem to relate to greater opportunity for stimuli for coughing to elude the barrier of the epiglottis. Alcohol in some individuals lowers the threshold to syncope or convulsions. The susceptibility to syncope in middle life may be related to the reduction of cerebral blood flow in these decades.

Medicolegal Aspects

Situations have arisen in which persons subject to tussive syncope have had episodes while driving an automobile and caused death to a pedestrian [40] or damage to property.[17e] Most of our patients have had sufficient warning to avert serious accidents, but two of them have voluntarily relinquished driving automobiles. To determine whether the defendant in the tort action has been guilty of negligence, the courts have set up the standard of a reasonable man. Under the majority common law rule, founding liability to a guest, on failure to exercise ordinary care, it is usually actionable for the host to fall asleep while engaged in the operation of the car, since, in the absence of special circumstances, he has the choice either to keep awake or to cease driving.[41]

The situation seems different where a pattern has been established, i.e., where a person has had enough attacks to demonstrate the possibility of another. According to Duff,[42] the occupant of an automobile may be held liable where the volitional act is apparently lacking. Specifically, this occurs when the actor drives an automobile knowing that he is subject to attacks

which may make the operation of the vehicle dangerous.[43] From the foregoing, it would seem part of the physician's responsibility to alert his patient to the legal implications in driving, if a pattern of cough syncope has been established.

Treatment

Treatment consists in eradicating the underlying cause of cough when feasible. Our case 2 had no recurrences after lobectomy for chronic bronchiectasis. Attempts to diminish the sensitivity of the cough reflex are indicated. Cocainization of particularly sensitive areas has met with success.[5e] Procaine block of the superior laryngeal nerve has been useful in stubborn situations.[44] Smoking and excess alcohol should be discouraged. In the obese, weight reduction should be urged. A trial of atropine in full doses is warranted, but has not been useful in our patients. No drug is capable of simultaneously directly offsetting the adverse effects of pulmonary hypertension and peripheral hypotension.

No therapy is indicated during the attack. Patients with self-limited causes of cough may be treated expectantly and optimistically. In those with serious cardiovascular disease, vigorous measures are indicated to forestall a fatality.

Summary

Cough syncope, not widely known to the American physician, has been observed in 25 instances recently. Characterized by sudden syncope following vigorous unproductive cough, it occurs in middle aged men who are robust and extroverted, and who indulge heavily in smoking, drinking and eating. Chronic pulmonary diseases—emphysema and bronchial asthma—are often present. The course of the disease is variable, paralleling the underlying respiratory disease. Although it is usually benign, fatalities have occurred in 1 to 2 per cent. The mechanism of the syncope is unproved. Treatment for the most part is symptomatic.

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LYMPHOCYTIC LEUKEMIA: AN ANALYSIS OF FREQUENCY, DISTRIBUTION AND MORTALITY AT THE UNIVERSITY OF CALIFORNIA HOSPITAL, 1913–1947 *

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In a previously published report,[1] data were presented and analyzed relative to the frequency, distribution and mortality of patients with myelocytic leukemia seen in three hospitals in San Francisco during the period 1910 to 1947, inclusive. The present communication presents similar data on patients with lymphocytic leukemia, 1913 to 1947, inclusive, although the source of the material is limited to the University of California Hospital.

The specific purposes of this study are (1) to analyze statistics relative to age at onset, sex, duration of illness and mortality of patients with acute and with chronic lymphocytic leukemia; (2) to note the possible changes that may have occurred in these statistics during the 35 year period, particularly in regard to the effects of therapy, and (3) to compare the data with similar reports available in the medical literature.

Materials and Methods

All clinical records of patients with lymphocytic leukemia were personally examined. The data were divided into three periods: patients seen from 1913 through 1929, from 1930 through 1939, and from 1940 through 1947 (table 1).

Cases were included on the basis of definitely established clinical diagnosis of lymphocytic leukemia. In all but one case (diagnosed by necropsy only), the clinical examination included study of the peripheral blood. Of the total 286 cases, bone marrow aspiration was performed in 109 and biopsy of a lymph node was obtained in 80. Follow-up was complete in 273 patients (95 per cent), of whom seven were alive on January 1, 1952. The diagnosis was confirmed by autopsy in 105 of the 266 patients known to be dead (39 per cent).

The cases were divided into two groups, acute and chronic. Sharp differentiation between acute and chronic lymphocytic leukemia and between

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subleukemic and leukemic leukemia is difficult if not impossible in many individual cases. For that matter, the designation of many cases of acute leukemia in children as lymphocytic or lymphoblastic is made more by exclusion than on the basis of sharp criteria regarding the cell of derivation. All that can be said is that, by the total clinical and hematologic criteria, all cases of granulocytic or monocytic types were excluded.

The differentiation between acute and chronic leukemia was made on the basis of rapid onset, fulminant course and the presence of lymphoblasts in the peripheral blood or bone marrow. The differences between acute and chronic lymphocytic leukemia appear to be more clear cut than in myelocytic leukemia. Only two of 137 patients with chronic lymphocytic leukemia were

TABLE I

Lymphocytic Leukemia; Total Data, University of California Hospital, 1913–1947, Inclusive

	1913–29	1930–39	1940–47	Total
Acute Lymphocytic Leukemia				
Number of Cases	26	30	93	149
Males	17	18	56	91
Females	9	12	37	58
Status, Jan. 1, 1952				
Dead	26	28	89	143
Alive	0	0	0	0
Unknown	0	2	4	6
Chronic Lymphocytic Leukemia				
Number of Cases	18	57	62	137
Males	13	43	42	98
Females	5	14	20	39
Status, Jan. 1, 1952				
Dead	17	54	52	123
Alive	0	0	7	7
Unknown	1	3	3	7

recorded as showing an acute exacerbation, whereas in chronic myelocytic leukemia approximately one fourth of the cases terminate in acute exacerbation.

The differentiation between subleukemic and leukemic leukemia, attempted primarily for statistical analysis of childhood leukemia, was made on the arbitrary basis of the presence of under or over 20,000 leukocytes per cubic millimeter in the peripheral blood at the initial examination.

The duration of the disease was determined from apparent clinical onset to death or latest follow-up in January, 1952. If there was a question as to whether the symptoms could have been due to leukemia, or if such symptoms were not continuous and progressive until the diagnosis was established, the date of diagnosis was taken as the date of onset. In 10 patients with chronic lymphocytic leukemia the diagnosis was made on routine blood ex-

amination upon admission for another, apparently unrelated condition. The date of onset in these patients was also taken as the date of diagnosis.

Differences between groups were analyzed by accepted statistical methods. Differences were considered "significant" if the probability was 0.05 or less that the difference could have occurred by chance. Some differences were great enough to have probabilities of 0.01 or less.

I. Acute Lymphocytic Leukemia

The cases of acute leukemia were divided into three periods (table 1). Analyses indicated, however, that there were no significant or consistent differences according to these periods relative to age at onset, sex ratio or mean

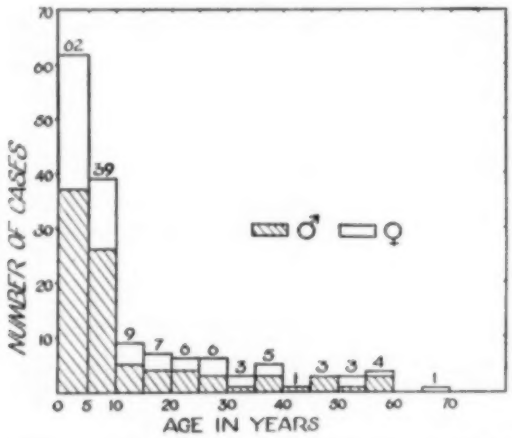

Fig. 1. Age at onset of 149 patients with acute lymphocytic leukemia.

duration of disease from onset to death. The data were therefore combined for presentation.

Sex: Of the total of 149 cases, 91 were males and 58 were females, a ratio of approximately 1.6 males to one female.

Age at Onset: The ages at onset are given in figure 1. Of the total, 62 cases (42 per cent) occurred before the age of five years, and 99 cases (66 per cent) occurred before the age of 10 years. The mean age at onset was 13.5 ± 1.2 years, and the median was 6.6 ± 1.5 years.

The ratio between males and females remains the same at all ages. The distribution of the cases plotted against the percentile distribution of the admissions to the University of California Hospital according to age is shown in figure 2.

Survival: The survival in months from clinical onset to death in the 149 cases of acute lymphocytic leukemia is given in table 2. Six of the patients

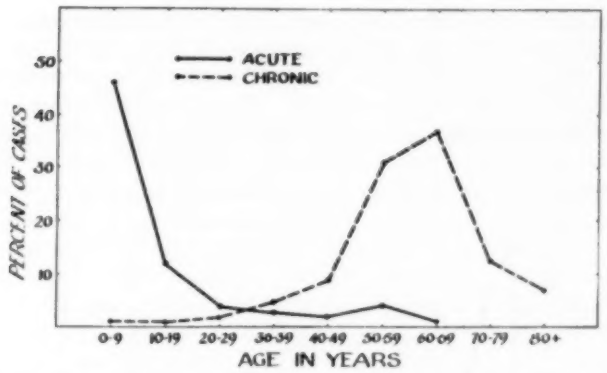

FIG. 2. Distribution of cases of lymphocytic leukemia, against the percentile distribution of admissions, by age, to the University of California Hospital.

were lost to follow-up, and one patient was diagnosed at autopsy. The exclusion of these seven patients does not affect the mortality curve to a significant degree, and these cases are included as living until the month of their latest follow-up. There were no significant differences in survival between males and females.

Analysis of survivals according to age at onset shows that patients in the age group five to 14 years lived longer than patients in the age group under five years, and over 15 years. At three and one-half months after onset, the survivals among patients of ages 0 to four years, five to 14 years,

TABLE II

Survival from Onset to Death in Acute Lymphocytic Leukemia by Major Forms of Treatment

Months After Onset		0.5	1.5	2.5	3.5	4.5	5.5	6.5	7.5	8.5	9.5	10.5	11.5	12.5
Total Number of Cases	149													
No. alive		146	134	110	86	63	47	35	32	21	11	10	10	7
Per cent alive		98.0	89.9	73.8	57.7	42.3	31.5	23.5	21.5	14.1	7.4	6.7	6.7	4.7
Standard error of per cent		±1.2	±2.5	±3.6	±4.1	±4.1	±3.8	±3.5	±3.4	±2.8	±2.1	±2.0	±2.0	±1.7
Radiation	45													
No. alive		45	42	35	27	19	13	8	7	4	1	1	1	0
Per cent alive		100.0	93.3	77.8	60.0	42.2	28.9	17.8	15.5	8.9	2.2	2.2	2.2	0
Standard error of per cent			±3.73	±6.2	±7.3	±7.4	±6.8	±5.8	±5.4	±4.2	±2.2	±2.2	±2.2	
Supportive	64													
No. alive		62	57	48	39	31	25	19	17	11	5	4	4	4
Per cent alive		96.9	89.1	75.0	60.9	48.4	39.1	29.7	26.6	17.2	7.8	6.2	6.2	6.2
Standard error of per cent		±2.2	±3.9	±5.4	±6.1	±6.2	±6.1	±5.7	±5.5	±4.7	±3.4	±3.0	±3.0	±3.0
Chemotherapy	9													
No. alive		9	9	8	6	5	3	3	3	1	1	1	1	0
"None"	31													
No. alive		30	26	19	14	8	6	5	5	5	4	4	4	3
Per cent alive		96.8	83.9	61.3	45.2	25.8	19.4	16.1	16.1	16.1	12.9	12.9	12.9	9.7
Standard error of per cent		±3.2	±6.6	±8.7	±8.9	±7.8	±7.1	±6.6	±6.6	±6.6	±6.0	±6.0	±6.0	±5.3

and 15 years and over were 52, 71 and 51 per cent, respectively, with the survival in the five to 14 year group being significantly higher than in the 0 to four year age group. At six and one-half months the survival percentages were 14, 35 and 23, respectively. Again, the survival in the five to 14 year age group was significantly higher than that in the 0 to four year age group.

Duration of Illness: The mean duration of illness from onset of all 149 patients was 5.4 ± 0.29 months; the median duration (the time at which

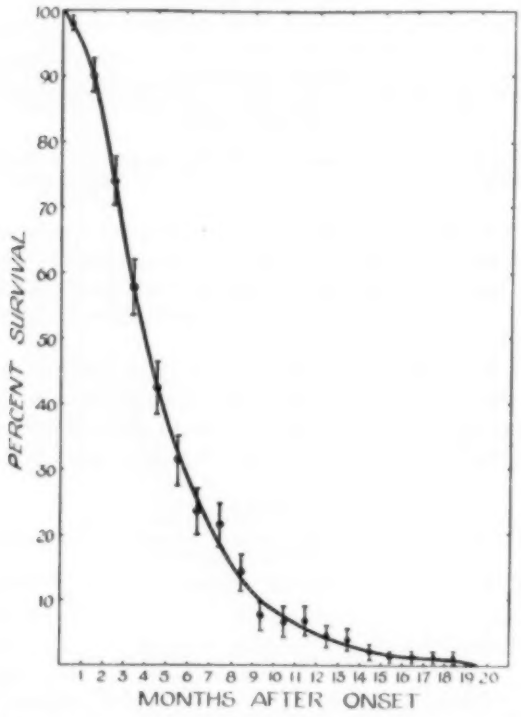

FIG. 3. Duration of illness in 149 patients with acute lymphocytic leukemia from clinical onset to death.

50 per cent of the cases are dead) was 4.5 ± 0.36 months (figure 3). Two patients lived for 18 months after the onset of illness, and all were dead at 19 months.

When the total leukocyte counts at the initial examination were considered, significantly longer survivals were found in patients of "subleukemic" (under 20,000) group. The mean duration of illness in 81 patients of the initially subleukemic group was 6.5 ± 0.42, whereas in 68 patients with initially higher leukocyte counts (over 20,000) the duration was 4.1 ± 0.32

months. The difference is accentuated when cases of the extreme groups are considered. Thus, of 35 patients with initial leukocyte counts of 5,000 or less, 11 survived the sixth month, whereas of 38 patients with initial leukocyte counts of over 50,000, only one survived the sixth month. The difference in six-month survivals between the two latter groups is statistically significant.

Effect of Treatment: Survival percentages are presented for cases receiving the major forms of treatment (table 2). Radiation therapy included administration of radiophosphorus as well as x-ray; a few of these patients also received Fowler's solution. Under "supportive" treatment were included patients who received transfusions and, after 1938, sulfanilamide or one of the antibiotic agents. Nine patients received chemotherapy: Fowler's solution, urethane, amine mustard or Aminopterin. The group of 31 cases recorded as receiving no treatment had no record of having had transfusions, antibiotics, chemotherapeutic agents or radiation.

There were no significant differences between the survival percentages of the patients in these treatment groups, and therefore no differential effect upon survival by these forms of treatment could be demonstrated in acute leukemia. It was found that the survival percentage at five months for patients who received supportive treatment was significantly greater than that for patients for whom no treatment was recorded. Actually, no conclusions may be drawn since all groups are relatively small. It is of interest that, although not significant, the survivals are higher in each successive month among patients receiving supportive treatment than among patients who received no treatment or who were treated with radiation.[2]

II. Chronic Lymphocytic Leukemia

The cases of chronic leukemia also were divided into three periods, 1913–1929, 1930–1939 and 1940–1947. Analyses indicated that there were no significant differences according to these periods relative to age at onset, sex ratio or mean duration of disease from onset to death. However, two characteristics similar to those found among patients with myelocytic leukemia were noted: a slightly greater proportion of males before 1940, and a higher mean age at onset after this date.

Sex: Of the total 137 cases, 98 were males and 39 were females, a ratio of approximately 2.5 males to one female.

Age at Onset: The ages at onset are given in figure 4. The peak frequency is during the sixth decade. The mean age of all cases is 54.3 ± 1.1 years. For the males, the mean age is 55.0 ± 1.3, and for females, 52.5 ± 2.2, a difference which is not significant. When the ratio of the number of patients with chronic lymphocytic leukemia to the corresponding age groups of the total hospital admission population was determined, there were proportionately more patients with this disease whose ages at onset fell into the seventh decade (60–69 years of age). These ratios are presented in figure 2.

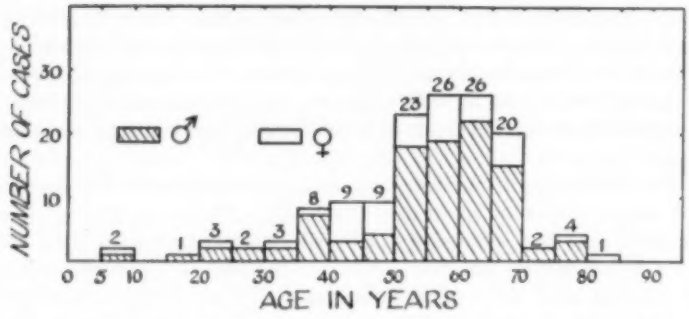

FIG. 4. Age at onset of 137 patients with chronic lymphocytic leukemia.

Survival: Survival in months from clinical onset to death in 137 cases of chronic lymphocytic leukemia is presented in table 3. Seven of the patients were lost to follow-up, and seven patients were alive at the last date considered in the analysis (January 1, 1952). Since the exclusion of these 14 patients does not affect the mortality curve to a significant degree, subsequent analyses are based on the total of 137 cases. The seven cases lost to follow-up are included up to the last month of latest known follow-up. There were no significant differences in survival between males and females. At three years after onset, 49 per cent of the males and 59 per cent of the females were alive; at five years, 24 per cent of the males and 28 per cent of the females were alive.

TABLE III

Survival from Onset to Death in Chronic Lymphocytic Leukemia by Major Types of Treatment

Years After Onset		1	2	3	4	5	6	7	8	9	10
All cases	137										
No. alive		109	90	71	45	34	20	10	7	5	5
Per cent alive		79.6	65.7	51.8	32.8	24.8	14.6	7.3	5.1	3.6	3.6
Standard error of per cent		±3.4	±4.1	±4.3	±4.0	±3.7	±3.0	±2.2	±1.9	±1.6	±1.6
X-ray only	68										
No. alive		57	44	35	19	15	9	4	3	2	2
Per cent alive		83.8	64.7	51.5	27.9	22.0	13.2	5.9	4.4	2.9	2.9
Standard error of per cent		±4.5	±5.8	±6.1	±5.5	±5.3	±4.1	±2.9	±2.5	±2.0	±2.0
X-ray, P^{32}	28										
No. alive		21	19	15	11	7	2	0			
Per cent alive		75.0	67.8	53.6	39.3	25.0	7.1				
Standard error of per cent		±8.2	±8.8	±9.4	±9.2	±8.2	±4.9				
X-ray, chemicals	18										
No. alive		15	14	11	9	9	7	5	3	2	2
No x-ray	23										
No. alive		16	13	10	6	3	2	1	1	1	1
Per cent alive		69.6	56.5	43.5	26.1	13.0	8.7	4.3	4.3	4.3	4.3
Standard error of per cent		±9.6	±10.34	±10.34	±9.2	±7.0	±5.9	±4.2	±4.2	±4.2	±4.2
Chemical agents	8										
No. alive		6	5	4	3	1	1	0			
"None"	15										
No. alive		10	8	6	3	2	1	1	1	1	1

Age at onset did not affect survival, there being no consistent or significant differences between the age groups. The three year survival percentage of 28 patients under 45 years of age was 46; for 33 patients between 45 and 54, 64; for 49 patients between 55 and 64 years, 47; and for patients 65 years or older, 52. At five years, the survivals were 21, 33, 26 and 15 per cent, respectively. Although the highest survival percentages are in the age group 45 to 54, none of the survivals differed significantly from those of other age groups except at the end of the first year between the age group 0–44 and 45–54 years (64 versus 91 per cent).

Analysis of the data according to the initial leukocyte count also failed to reveal consistent or significant differences, in contrast to the findings among patients with acute leukemia. Of 42 patients with initial leukocyte counts

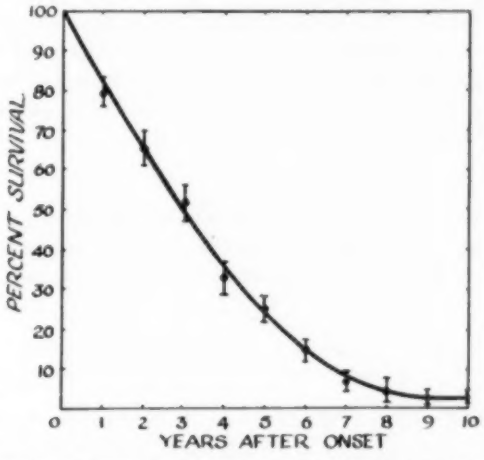

FIG. 5. Duration of illness in 137 patients with chronic lymphocytic leukemia from clinical onset to death.

of under 20,000, 48 per cent were alive at three years; of 95 patients with initial leukocyte counts of over 20,000, 54 per cent were alive at three years, a difference which is not significant. Of the extreme groups, 18 patients had initial leukocyte counts of under 10,000, and nine were alive at three years; of 43 patients with initial leukocyte counts of over 100,000, 23 (or 54 per cent) were alive at three years.

Duration of Illness: The mean duration of illness of 132 patients, not including five cases who lived for over 10 years, was 37 ± 2.2 months, approximately three years (figure 5). The median duration was also three years (36 ± 2.7 months). If the five cases which survived 10 years or more are included, the mean number of months duration of illness increases to three and one-half years (42 ± 3.0 months), but the median remains at three years.

Effect of Treatment: Survival of patients grouped according to the major forms of treatment is presented in table 3. All but 23 patients received some form of radiation, by means of x-ray or radiophosphorus. It is obvious that no analysis is possible and no conclusions relative to the effects of treatment can be drawn, because the type of radiation, the period of time over which it was given, the total dosage and the sites to which it was administered varied greatly. It was found that the survival percentage of the 23 patients who received no radiation was not significantly lower at three and five years than the survival percentage of 68 patients who received x-ray alone.

It is of interest that the total survival was no better during recent years than before 1930. Thus, of 57 patients seen between 1930 and 1939, 51 per cent were alive at three years and 25 per cent were alive at five years. Of 62 patients seen after 1940, the survivals were 50 and 21 per cent, respectively. It may be concluded that the medical management available after 1940 at this hospital has not yielded significant improvement in total survival. This general conclusion is the same as that made in the preceding study on chronic myelocytic leukemia.

Discussion

Acute Lymphocytic Leukemia: The data presented in this investigation regarding patients with acute lymphocytic leukemia coincide closely with similar data available in the literature (table 4). Perhaps the only dis-

Table IV

Comparative Data on Acute Lymphocytic Leukemia

Author and Reference	Region	Dates	Cases No.	Ratio of Males to Females	Mean Survival Months
Cooke [3]	Missouri	1918–33	50	2:1	3.6
Booth [4]	Minnesota	1930–38	40	2:1	4.8
Falkenstein [5]	Iowa	to 1943	61	2:1	4.3
Sullivan [6]	Dist. Columbia	1938–47	63	2:1	4.0
Dale [7]	New York	1932–48	39	1:1	4.0
Southam [8]	New York	1926–48	150	2:1	4.8
Rodgers [9]	Toronto	1932–47	150	2:1	4.1
Poncher [10]	Chicago	1932–52	48	2:1	5.4

crepancy is the somewhat longer mean duration of the disease of 5.4 months, as compared with the durations of 3.6 to 4.8 months given by all but one of the reports summarized in table 4. The difference between the duration of the disease reported here was found to be statistically significant when compared with the duration of 4.8 months recorded by Southam et al.[8] and of 4.1 months published by Rodgers et al.[9] The mean figure is identical, however, to the one given by Poncher et al.[10] on 48 cases.

The thorough statistical analysis of data by two groups of investigators permits direct comparisons. Rodgers et al.[9] found slightly better survivals

among children between the ages of seven and nine years than among patients of other ages. In our data, significantly higher percentage survivals were consistently found at three and one-half through eight and one-half months among children in the age group of five to 14 years, as compared with children in the age group under five years. On the other hand, Southam et al.[8] found no correlation with age. There is agreement that survival is longer in the patients with low white blood cell counts than in patients with high leukocyte counts.

The mean survival of all patients with acute lymphocytic leukemia will be influenced by the proportion of cases in various age groups and by the proportion of patients with low leukocyte counts. Consideration should be given to age of patient and leukocyte counts when comparing duration of the disease in groups of patients who now are receiving treatment with antifolic acid compounds [11] and with cortisone and adrencorticotropin.[12] There now

TABLE V

Comparative Data on Chronic Lymphocytic Leukemia

Author and Reference	Region	Date	No. of Cases	Ratio of Males to Females	Mean Age in Years at Onset	Mean Survival in Years
Ward [13]	England	to 1917	84	3:1	52	—
Minot [14]	Boston	1898–1923	92	3:1	52	3.5
Leavell [15]	New York	1917–1934	49	3:1	53	3.6
Wintrobe [16]	Baltimore	1926–1938	47	5:1	57	2.3
Kirschbaum [17]	Chicago	1929–1941	26	5:1	57	—
Reinhard [18]	St. Louis	1936–1946	30	2:1	56	—
Lawrence [19]	Berkeley	1936–1947	100	2:1	53	4.5
Osgood [20]	Portland	1941–1951	102	3:1	58	7.0*

* Estimated.

appears to be real evidence that the use of the newer chemotherapeutic agents in acute leukemia in childhood significantly prolongs the life of the patients.[10]

Chronic Lymphocytic Leukemia: There are but few papers that present data concerning chronic lymphocytic leukemia in a systematic fashion which allows direct comparison (table 5). For example, only eight reports [13-20] were found in which the age distribution is given in five or 10 year age groups. Moreover, it is surprising that the respective series comprise relatively small numbers of cases. Only the present report, the report of Lawrence et al.[19] and that of Osgood and Seaman [20] reach 100 cases. A number of cases of the present report were also included in the report of Lawrence et al.,[19] but the extent of duplication is unknown.

In general, the impression that patients with chronic lymphocytic leukemia seen in recent years appear to be older on the average than formerly is substantiated by the literature. Ward [13] and Minot and Isaacs [14] report a mean age of approximately 52 years. The mean ages reported from series of patients seen after 1935 are higher by three years than the mean ages of series of patients seen before 1935. This is consistent with similar findings

reported for chronic myelocytic leukemia.[1] This fact is also reflected in figures on mortality from leukemia made available by the statistics of the Bureau of the Census.[21] There seems to be little evidence of a shift in sex ratio during recent years toward a greater proportion of females.

Only the classic paper of Minot and Isaacs,[14] and the recent reports of Lawrence et al.[19] and of Osgood and Seaman,[20] present data in sufficient detail with respect to duration of illness to allow statistical comparisons. Other reports in the literature are limited to overall statements of mean survival.

The only paper that contains anything resembling a control group for comparison with cases treated by radiation is the one by Minot and Isaacs.[14] No difference was present between 50 patients treated with radiation and 30 patients who did not receive such treatment, and the overall mean duration of illness was three and one-half years. Figures of three to 3.6 years as the average survival of all cases are to be found in other reports, all of which note that approximately 15 per cent of the patients live for five years or longer. Individual cases may live as long as 25 years.[22] The mean duration of life reported by Lawrence et al.[19] with 24 patients still living was four and one-half years (54 months), which is significantly longer than the three and one-half years reported here. Whether radiophosphorus is to be given credit for this prolongation of life or whether the group treated by Lawrence et al.[19] is comparable to the usual hospital population with chronic lymphocytic leukemia, cannot be determined from information now available.

The recent report of Osgood and Seaman [20] presents data and a statistical evaluation of 163 patients with chronic leukemia, including 102 patients with chronic lymphocytic leukemia, treated by "titrated, regularly spaced total body radioactive phosphorus, or roentgen irradiation." Since 55 patients with chronic lymphocytic leukemia were still alive, the ultimate survivals from onset and after therapy were predicted by the "method of maximum likelihood," giving a mean of seven years from onset. The survival of 48 per cent of the patients has been predicted as five years or longer after the onset of leukemia. The authors stress the fact that meticulous periodic estimations of the patients, with prompt treatment for intercurrent infections and other unrelated associated diseases, is an important aspect of total management of their patients. The values for survival reported by Osgood and Seaman are higher than any previously available for a comparable group of patients, and it is hoped that their findings can be reproduced in other medical centers.

Summary

Statistics are presented regarding the age at onset, sex, duration of illness and mortality of 149 patients with acute lymphocytic leukemia and 137 patients with chronic lymphocytic leukemia seen at the University of California Hospital, 1913 to 1947, inclusive. The data are compared with

eight similar reports in the literature on acute leukemia and eight similar reports on chronic leukemia.

The age and sex distribution and duration of illness in acute lymphocytic leukemia have remained fairly constant during the period of study. There may have been a shift toward a higher age at onset among patients with chronic lymphocytic leukemia, but the sex distribution and duration of illness have remained fairly constant.

The mean duration of illness from onset to death in 149 cases of acute lymphocytic leukemia was found to be 5.4 months. The duration of illness was longer among the age group five to 14 years than in age groups 0 to four years and 14 years and over, and was longer in patients with initially low leukocyte counts than in patients with high leukocyte counts.

The mean duration of illness from onset to death in 137 cases of chronic lymphocytic leukemia was found to be 42 months. No differences were present relative to age at onset or the initial leukocyte count.

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SOME CLINICAL CAPRICES OF MULTIPLE MYELOMA: 15 CASE REPORTS FROM A STUDY OF 75 CASES *

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Both the title and the general scheme of this presentation, although inevitably modified, are acknowledged to be in deliberate emulation of the superb article by William S. Middleton [1] published in 1937 on the subject of Hodgkin's disease. They, the title and the scheme, and the attitude as well, are as felicitous in their application to multiple myeloma as they were to Middleton's original use in relation to Hodgkin's disease.

Although the disease has been adequately described [2] for over a century, resistance to treatment has engendered, directly, therapeutic pessimism, and, indirectly, a lack of interest and mistaken diagnoses. The diagnosis of multiple myeloma nevertheless is being made increasingly, although often quite by accident, as a consequence of routine roentgenographic examinations of the chest, the frequent determination of serum protein, and the widespread use of marrow examinations in the study of unexplained anemia. Growing diagnostic alertness has further improved recognition of the disease which, if not common, is certainly not rare.

There have been sufficient reports of the classic signs and symptoms: bone lesions with pain and pathologic fractures, elevations in the various globulin fractions of the serum, Bence Jones proteinuria, renal impairment —all the outcome of the keystone of the disease, the focal or diffuse abnormal overgrowth of plasma cells. By reason of this common feature of multiple myeloma, examination of the marrow is diagnostically and prognostically a necessity, although, as case 13 illustrates, not invariably conclusive.

As Middleton has said of Hodgkin's disease, so might it well be said of multiple myeloma: "Few clinical conditions conform more closely to the accepted descriptions than does the typical case. . . . At the same time there is no disease with a more diversified range of clinical expression. On one hand these variants may result from the overwhelming predominant emphasis upon some common or uncommon feature of the disease. Again some clinical vagary may so distort the picture as to render its diagnosis extremely difficult. . . . Clearly the clinical pattern must not be too sharply drawn or many cases will escape early recognition." It was such thoughts as these that stimulated the present study, for the established criteria of diagnosis will insure detection of the classic case but not the capricious one. The

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intent here, then, is to emphasize how and why multiple myeloma was suggested in this series, irrespective of the presenting symptoms, which were at times vague, far removed, even misleading, and not at all pathognomonic in themselves.

In this paper 15 cases have been selected for detailed description in order to exhibit the diversity of guises in which multiple myeloma may make its appearance.

Case Reports

Case 1. Paraplegia. A Negro male, aged 53, was admitted to Cook County Hospital on December 1, 1951, presumably because of cerebral metastases. The patient reported that he had become ill the previous February with pain in the right and left anterior iliac region which he noted at first only on jarring or running. By June pain was felt high in the thoracic region, and later there was pain low in the back, made worse on coughing or straining. At that time the patient was treated elsewhere and was given a back brace which temporarily improved walking. Low back pain persisted on movement, however, and was greatly increased on coughing.

The patient did not appear ill on admission except for marked paresis and atrophy of both legs. In addition to the presenting symptoms, the only points worth noting on physical examination were: pale conjunctivae, mucosal pallor, papillated tongue, and asymmetry of the thyroid gland with a nodule in the right lobe. Coarse breath sounds and râles were audible over the right base. There was a loss of deep reflexes on the right side, but sensation was intact.

Examination of the blood showed hemoglobin, 6.7 gm. (43 per cent); red blood cells, 2.30 million; white blood cells, 4,800; polymorphonuclear leukocytes, 44 per cent; bands, 8 per cent; lymphocytes, 25 per cent; monocytes, 5 per cent; eosinophils, 6 per cent; basophils, 2 per cent; promyelocytes, 1 per cent; myelocytes, 2 per cent; metamyelocytes, 7 per cent; nucleated red blood cells, 8 per 100 leukocytes. Platelets were adequate.

Chemical analysis of the blood showed acid phosphatase, 0.2 Bodansky units; alkaline phosphatase, 2.8 Bodansky units; phosphorus, 4.8 mg. per cent; total protein, 10 gm. per cent; an albumin-globulin ratio of 2.8/7.2 gm.

Urinalysis was negative for Bence Jones protein.

The marrow on examination was markedly hypercellular. Megakaryocytes were decreased in number. There was a diffuse replacement of the marrow by mature plasma cells, diagnostic of multiple myeloma.

Roentgenograms of the ribs, pelvic bones, vertebrae and skull showed characteristic punched-out lesions of the skull and pelvis.

Comment: The reversed albumin-globulin ratio, revealed during chemical analysis of the blood, as well as anemia and a leukemoid reaction in the peripheral blood, suggested the need for study of the marrow, which proved to be diagnostic. Roentgenograms were also substantiating.

Case 2. Epistaxes. A Negro male, aged 48, was admitted to Cook County Hospital on January 10, 1952, because of severe headaches, weakness and repeated nosebleeds of sudden onset six days previous to admission. Cough, fever and general malaise followed. There had been a 20 pound loss of weight in six months. The diagnosis in the admitting room was cryptogenic fever.

Three months earlier the patient had been told that a roentgenogram of the chest showed enlargement of the heart. There was no previous or family history of bleeding. The patient had undergone treatment for syphilis in 1941.

The patient was well developed, well nourished, alert and coöperative. His blood pressure was 120/50 mm. of Hg; pulse, 78; respirations, 20; temperature, 100° F. There was an equivocal diastolic murmur. The conjunctivae were pale, and there were bilateral nasal blood clots. Crepitant râles were heard in the lungs, with an occasional wheeze in the left base posteriorly. The heart was enlarged 3 cm. at the apex.

The blood count on the day of admission showed: hemoglobin, 6.0 gm. (39 per cent); red blood cells, 2.05 million; white blood cells, 3,200; polymorphonuclear leukocytes, 66 per cent; bands, 7 per cent; lymphocytes, 24 per cent; monocytes, 2 per cent; Türk's cell, 1 per cent; nucleated red blood cells, 6 per 100 white blood cells. Platelets were adequate.

Chemical analysis of the blood showed total protein, 9.0 and 10.8 gm. per cent; albumin-globulin ratios, 4.4/4.6 and 4.3/6.5; alkaline-phosphatase, 2.3 Bodansky units; phosphorus, 4.9 mg. per cent; gamma globulin, 5.54 mg. per cent; thymol turbidity, 13.0 units; nonprotein nitrogen, 34 mg. per cent.

Urinalysis was negative for Bence Jones protein but showed a 4 plus albumin.

Because of marked anemia, leukopenia and nucleated red blood cells in the peripheral blood, the marrow was examined and found to contain a significant increase in mature plasma cells, a finding compatible with multiple myeloma.

Roentgenographic examination was unrevealing.

Comment: Rheumatic heart disease and pneumonia comprised the first diagnosis after physical examination. The laboratory report of severe anemia, leukopenia and nucleated red blood cells, however, indicated the advisability of a marrow study, which revealed unequivocal multiple myeloma. The elevated blood proteins and globulins in particular were confirmatory.

Case 3. Anemia. A Negro female, aged 51, was admitted to Cook County Hospital on September 8, 1951, through the surgery clinic, where it had been found that she was anemic following a thyroidectomy performed the previous month. There was a well healed thyroidectomy scar. The only presenting symptoms other than known anemia were edema of the legs, emaciation, and pale conjunctivae and tongue.

The blood count on the day of admission gave: hemoglobin, 4.3 gm. (28 per cent); red blood cells, 2.01 million; white blood cells, 2,450; polymorphonuclear leukocytes, 71 per cent; bands, 12 per cent; lymphocytes, 8 per cent; monocytes, 2 per cent; eosinophils, 1 per cent; basophils, 6 per cent. The Kahn reaction was positive.

Chemical analysis of the blood showed nonprotein nitrogen, 24 mg. per cent; total protein, 7.6 gm. per cent; alkaline phosphatase, 3.0 Bodansky units; albumin-globulin ratio, 4.1/2.9; calcium, 8.2 mg. per cent; phosphorus, 4.6 mg. per cent.

Urinalysis was negative for Bence Jones protein but showed 2 plus albumin.

A marrow study was made on September 15. This revealed moderate cellularity with normal megakaryocytes. Nucleated red blood cell-white blood cell ratio was approximately 1:3. Erythropoiesis was normoblastic. Granulopoiesis showed a marked increase in plasma cells, many of which were immature, and a slight increase in eosinophils. Many phagocytic cells containing iron were seen.

The findings were thought to be compatible with multiple myeloma, and it was suggested that roentgenographic bone survey, albumin-globulin ratio and Bence Jones protein determinations of the urine be made. These were found to be normal.

Succeeding blood counts were made on October 3 and 18, with the following results: For the first and second dates respectively: hemoglobin, 3.7 gm. (24 per cent) and 6.7 gm. (43 per cent); red blood cells, 1.87 million and 2.80 million; white blood cells, 2,750 and 1,250; polymorphonuclear leukocytes, 79 and 72 per cent; bands,

8 and 17 per cent; lymphocytes, 6 and 2 per cent; monocytes, 7 and 8 per cent; and Türk's cell, 1 per cent (the last reported on the first date only).

A second marrow study (made on October 26) yielded the following: moderate cellularity; normal megakaryocytes; nucleated red blood cell to white blood cell ratio of approximately 1:4; normoblastic erythropoiesis; marked increase in plasma cells occurring in clumps, many with bilobed nuclei. The marrow findings were now considered compatible with multiple myeloma.

Roentgenograms were normal.

Comment: The first diagnostic impressions had been of a possible lymphatic leukemia, carcinoma of the thyroid with extensive metastases, myxedema or possible multiple myeloma. The unexplained anemia indicated the need for a study of the marrow, which ultimately established the diagnosis.

Case 4. Pain in the hands. A white male, aged 54, was admitted on March 11, 1952. Pain, burning, coldness and numbness of the hands with difficulty in picking up objects had been present for two weeks.

The patient had had difficulty in breathing for the previous six weeks, as well as pedal edema for two weeks and pain across the chest and back for three weeks. The pain was sharp in both hands, the back and the feet, and was accompanied by a feeling of weakness.

The blood pressure was 190/90 mm. of Hg; temperature, 100° F.; pulse, 120. There was evidence of nosebleed and, on further questioning, epistaxes were found to have been frequent for six months. There was hyperflexion of the hands, and seborrheic dermatitis was present. Wheezes were heard in both lungs.

The blood count gave: hemoglobin, 8.4 gm. (54 per cent); red blood cells 3.64 million; white blood cells, 9,950; polymorphonuclear leukocytes, 85 per cent; bands, 3 per cent; lymphocytes, 4 per cent; monocytes, 3 per cent; eosinophils, 5 per cent. The sedimentation rate was 20 mm. per hour; hematocrit, 31 per cent.

Because of an unexplained 4 plus albumin on urinalysis, a Bence Jones protein determination was made and was found positive.

Chemical analysis of the blood revealed: total protein, 7.0 gm. per cent; albumin-globulin ratio, 4.8/2.2; alkaline-phosphatase, 1.6 Bodansky units; acid phosphatase, 0.1 Bodansky unit; phosphorus, 3.8 mg. per cent; nonprotein nitrogen, 40 mg. per cent.

Examination of the marrow showed it to be moderately hypercellular. Megakaryocytes were decreased in number. The marrow was virtually replaced by mature plasma cells which were present in syncytium. The findings were diagnostic of multiple myeloma.

A roentgenographic survey revealed defects of the third, fifth and sixth vertebrae, and multiple small punched-out areas of the skull.

Comment: An unexplained 4 plus albuminuria called for a Bence Jones protein determination, which was found to be positive. Roentgenologic evidence supported the supposition, and the marrow study confirmed the diagnosis.

Case 5. Hip pain. A Negro female, aged 55, was admitted to Cook County Hospital on August 18, 1951, because of severe pain in the left hip of 10 months' duration, with gradual development of pain in the right hip which radiated to the lumbosacral area. Pain had increased so much that the patient had been unable to walk for a week, it was constant and not dependent on motion. There had been a

10 pound loss of weight during a six month period. Questioning revealed a history of nosebleeds during two or three day periods for the last four years.

The patient was fairly well developed but poorly nourished and appeared chronically ill. Râles were heard in the left base. There was pain on compression of the spine and on pressure over the upper femur. The blood pressure was 130/80 mm. of Hg.

The blood count on the day of admission gave: hemoglobin, 6.8 gm. (44 per cent); red blood cells, 2.51 million; white blood cells, 4,750; polymorphonuclear leukocytes, 60 per cent; bands, 6 per cent; lymphocytes, 31 per cent; monocytes, 3 per cent. The sedimentation rate was 7 mm.

Urinalysis showed 2 plus albumin. The Bence Jones protein determination was negative.

Chemical analysis of the blood showed: total protein, 12.6 gm. per cent; albumin-globulin ratio, 3.1/9.5; gamma globulin, 6.9 and 7.96 gm. per cent; calcium, 12.5 mg. per cent; phosphorus, 5.9 mg. per cent; alkaline-phosphatase, 1.2 Bodansky units; uric acid, 9.0 mg. per cent; nonprotein nitrogen, 99 mg. per cent; sugar, 105 mg. per cent; creatinine, 3.8 mg. per cent.

The marrow was very hypercellular, with a great decrease in megakaryocytes. There was a diffuse replacement of the marrow by sheets of mature plasma cells. The findings were considered diagnostic of multiple myeloma.

A roentgenographic survey revealed small radiolucent areas, and punched-out lesions of the ribs, clavicles, pelvis, skull and vertebrae.

Comment: Because of the type of bone pain, loss of weight, and the severity of the anemia, multiple myeloma was suggested and was confirmed on marrow examination and by the marked elevation of globulin. The diagnosis in the admitting room had been "arthritis."

Case 6. Back pain and marked weakness. A Negro male, aged 66, was admitted to Cook County Hospital on October 18, 1950, because of weakness and low back pain of many months' duration. In January of the same year the condition had been diagnosed elsewhere as arthritis.

The patient appeared poorly nourished and emaciated, and there was poor tissue turgor. He was not able to give an adequate history because of extreme weakness. The admitting room diagnostic impression was "leukemia."

A blood count on the day of admission showed: hemoglobin, 12.5 gm. (80 per cent); red blood cells, 4.18 million; white blood cells, 7,000; polymorphonuclear leukocytes, 70 per cent; lymphocytes, 24 per cent; monocytes, 6 per cent.

Urinalysis gave 2 plus albumin and a positive Bence Jones protein determination.

Chemical analysis of the blood showed nonprotein nitrogen, 68 mg. per cent; creatinine, 1.7 mg. per cent; total protein, 9.0 gm. per cent; albumin-globulin ratio, 2.3/6.7; alkaline-phosphatase, 3.5 Bodansky units; thymol turbidity, 1.2 units; gamma globulin, 5.06 gm. per cent.

Examination of the marrow showed that it was almost entirely replaced by plasma cells, diagnostic of multiple myeloma.

Roentgenographic survey showed multiple radiolucent areas of the skull.

Comment: The history of back pain and the significant increase in globulin first suggested multiple myeloma. This was confirmed by Bence Jones proteinuria and the marrow findings.

Case 7. Albuminuria. A Negro male, aged 47, was admitted to Cook County Hospital on May 1, 1951, because of a 4 plus albuminuria found on routine physical

examination. The patient had had nocturia for four months, his appetite had been poor, but he had noted no loss in weight.

Physical examination was not notable.

The blood count gave: hemoglobin, 8.1 gm. (52 per cent); red blood cells 2.71 million; white blood cells, 2,000; polymorphonuclear leukocytes, 38 per cent; bands, 10 per cent; monocytes, 1 per cent; lymphocytes, 50 per cent; basophils, 1 per cent.

Urinalysis showed 4 plus albumin. Because multiple myeloma was considered in the differential diagnosis, a test was made for Bence Jones proteinuria, which was found to be present.

Roentgenograms of the skull showed many osteolytic lesions.

Chemical analysis of the blood gave nonprotein nitrogen, 28 mg. per cent; total protein, 7.3 gm. per cent; albumin-globulin ratio, 4.3/2.7.

The appearance of the marrow was diagnostic of multiple myeloma.

Case 8. Hematuria. A white male, aged 66, was admitted to the Cook County Hospital on November 26, 1951, because of hematuria which had been occurring for four days and because of substernal pain and dyspnea.

The patient had been examined the previous May, when the diagnosis of myeloma was suggested, but at that time the marrow study failed to substantiate the diagnosis and he was discharged with a diagnosis of hyperproteinemia.

The patient's blood pressure on admission was 200/100 mm. of Hg; temperature, 97° F.; pulse, 80; respirations, 24. The tongue was papillated. There was a systolic murmur at the base. The liver was enlarged, and there was tenderness over the sternum and the sixth rib. Urinalysis showed 2 plus albumin, many red blood cells, a few white blood cells, and a positive Bence Jones reaction.

The blood count showed: hemoglobin, 11.7 gm. (75 per cent); red blood cells, 4.32 million; white blood cells, 5,850; polymorphonuclear leukocytes, 47 per cent; bands, 4 per cent; lymphocytes, 24 per cent; monocytes, 10 per cent; eosinophils, 5 per cent.

Chemical analysis of the blood revealed: total protein, 10.8 gm. per cent, with an albumin-globulin ratio of 2.9/7.9; gamma globulin, 3.86 gm. per cent; nonprotein nitrogen, 43 mg. per cent; phosphorus, 4.1 mg. per cent; cholesterol, 112 mg. per cent; alkaline-phosphatase, 2.7 Bodansky units; thymol turbidity, 1.2 units.

Roentgenographic examination of the skull and chest showed lesions typical of multiple myeloma.

The marrow on December 4 was largely replaced by plasma cells, consistent with multiple myeloma.

Comment: Multiple myeloma was suggested because of the elevated blood proteins and the reversed albumin-globulin ratio. This was substantiated by the lesions of the skull, and confirmed on examination of the marrow.

Case 9. Spontaneous fracture. A white male, aged 70, was admitted to the Cook County Hospital on December 2, 1950, with an admitting room diagnostic impression of hypernephroma with metastases. The patient stated that he had developed a sudden low back pain in February, 1949, while lifting an ice box. Roentgenograms at that time showed a fracture of the left tenth rib, as well as a compression fracture of the twelfth thoracic, less so of the seventh and eighth thoracic vertebrae. Since September, 1950, the patient had had pain in the chest and flank, still attributed to trauma.

The blood pressure was 122/70 mm. of Hg. There had been a loss of weight from 130 to 85 pounds. The patient was emaciated and had pain on motion. There were swelling and tenderness of the right tenth rib in the posterior axillary line.

Nodules could be palpated in the abdomen. The prostate was small. The spine was tender to fist percussion.

The blood count showed: hemoglobin, 10.4 gm. (67 per cent); red blood cells, 3.80 million; white blood cells, 6,400; polymorphonuclears, 70 per cent; lymphocytes, 24 per cent; monocytes, 4 per cent; eosinophils, 2 per cent.

Urinalysis showed a 4 plus albumin and gave a positive reaction for Bence Jones protein.

Chemical analysis of the blood showed total protein, 9.0 gm. per cent, with an albumin-globulin ratio of 2.8/6.2; gamma globulin, 4.56 gm. per cent; nonprotein nitrogen, 48 mg. per cent; thymol turbidity, 1.4 units; phosphorus, 3.6 mg. per cent; alkaline-phosphatase, 4.4 Bodansky units; acid phosphatase, 0.1 Bodansky unit.

Roentgenographic survey of the spine showed osteoporosis, and there were suggestive radiolucencies of the ribs and right humerus. There was a compression fracture of the twelfth thoracic vertebra.

Examination of the marrow showed it to be almost entirely replaced by mature plasma cells occurring in sheets.

Comment: The diagnosis of multiple myeloma was not considered until the elevated protein was found. Roentgenograms, marrow changes and Bence Jones proteinuria confirmed the diagnosis.

Case 10. Uremia. A white male, aged 38, was admitted on May 16, 1949, because of pain in the ribs, back and thigh.

The patient reported a year's history of "muscle strains all over the body." He had had pleurisy the previous fall, when he was confined to bed for six weeks. Severe pain in the hip followed, and his condition had deteriorated rapidly with extension of severe pain to the back and ribs.

The patient was alert but pale and apprehensive and resisted examination. He was poorly nourished. The blood pressure was 160/85 mm. of Hg; temperature, 101° F.; pulse, 124; respirations, 22. There were raised hard areas on the sternum which the patient said had appeared after his fall a week previously. There was some bone tenderness of the ribs and lower sternum, especially on motion.

The blood count showed: hemoglobin, 7.6 gm. (49 per cent); red blood cells, 2.59 million; white blood cells, 8,600; polymorphonuclear leukocytes, 54 per cent; bands, 16 per cent; lymphocytes, 11 per cent; monocytes, 8 per cent. There were also 6 per cent plasma cells, 3 per cent myelocytes, and 2 per cent metamyelocytes.

Urinalysis showed 3 plus albumin but was negative for Bence Jones protein.

Chemical analysis of the blood revealed nonprotein nitrogen, 204 mg. per cent; creatinine, 16.5 mg. per cent; total protein, 6.8 gm. per cent; albumin-globulin ratio, 4.6/2.2; phosphorus, 8.2 and 9.7 mg. per cent; acid phosphatase, 0.2 Bodansky unit; alkaline phosphatase, 1.7 Bodansky units.

A roentgenologic survey showed lesions of the skull and pelvis suggestive of multiple myeloma. No definite spicules of marrow were obtained on aspiration. In scattered groups of cells, however, there was an increase in plasma cells compatible with multiple myeloma.

Comment: The diagnosis underlying the presence of uremia was not at first evident, but because of anemia with a blood count in which 6 per cent plasma cells were reported and because of the multiple bone tenderness and raised areas on the sternum, multiple myeloma was considered and was confirmed on marrow and roentgenologic study.

Case 11. Edema of face and legs. A white male, aged 61, was admitted to the Cook County Hospital on March 7, 1947, because of swelling of the face and legs

of two weeks' duration, and pain in the small of the back which radiated around to the umbilicus. He reported weakness and fatigue of three months' duration, as well as a dull persistent ache low in the back. The patient had had slight epistaxes and poor appetite for three months, pain in the lower left side of the chest on coughing, and nocturnal frequency. He appeared to be chronically ill. Blood pressure was 162/70 mm. of Hg. There was a systolic murmur heard over the entire precordium, equivocal over the left side of the heart border. There were retinal hemorrhages throughout the fundi.

The diagnostic impression in the admitting room was "chronic glomerulonephritis."

The blood count on March 8, 1947 gave: hemoglobin, 4.8 gm. (31 per cent); red blood cells, 1.80 million; white blood cells, 13,700; polymorphonuclear leukocytes, 55 per cent; bands, 32 per cent; lymphocytes, 9 per cent; myelocytes, 1 per cent; irritation cell, 1 per cent; monocytes, 2 per cent; 2 nucleated red blood cells per 100 white blood cells.

Urinalysis was negative for Bence Jones protein, but there were 4 plus albumin and many hyaline and granular casts.

Chemical analysis of the blood revealed: auto-agglutination; nonprotein nitrogen, 68 mg. per cent; creatinine, 4.2 mg. per cent; total protein, 10.8 gm. per cent; albumin, 3.4; globulin, 7.4; phosphorus, 5.95 mg. per cent; alkaline phosphatase, 2.45 Bodansky units; acid phosphatase, 0 Bodansky units.

A roentgenographic survey showed infiltration in the clavicle and ribs, moderate thickening of the middle third of the tibial shaft, and irregular osteolytic lesions of the skull, zygoma and pelvis, without surrounding bone reaction. Similar lesions were seen in the hip and neck of the femur. There was a fracture of the midportion of the right eleventh rib, and there was left pleural effusion.

The marrow was markedly hypocellular. Occasional collections of primitive cells were encountered which were for the most part syncytial in arrangement and resembled metastatic carcinoma cells. In areas in which the cells were found in isolated groups, they closely resembled sarcoma cells. The diagnosis of myeloma was, however, finally reached on analysis of the whole material.

Comment: The distribution of edema at first suggested nephritis. Severe anemia, hypocellular marrow and the appearance of the cells in the marrow were reminiscent of metastatic carcinoma; however, the typical changes in the skeletal system and the changes in serum globulin finally established the correct diagnosis.

Case 12. Swelling of the jaw. A white male, aged 47, first entered the Cook County Hospital on September 10, 1946, because of a swelling of the left side of the mandible which had been present for three months. This was painful and steadily increasing in size. Three weeks before, some teeth had been extracted because of a presumed abscess. This had had no effect on the swelling. A roentgenogram of the jaw showed a destructive process of the mandible. This was curetted on September 12 and found to be due to a plasma cell myeloma.

The patient was re-admitted to the hospital on December 18, 1947, at which time he told of having had "flu" six weeks prior to admission. Following this he had continued to have pain in the ribs. Three days before admission he developed a recurrent, nonproductive cough, chill and fever. The pain in the ribs continued and he was "sore all over."

On examination the blood pressure was 140/90 mm. of Hg; temperature, 99.8° F.; respirations, 20; pulse, 98. The pharynx was injected, the chest was emphysematous, with a few bilateral basal râles, and the liver edge was 6 cm. below the costal margin.

On December 19 the blood count was 8.4 gm. (54 per cent); red blood cells, 3.08 million; white blood cells, 16,700; polymorphonuclears, 91 per cent; lymphocytes, 5 per cent; monocytes, 3 per cent; basophils, 1 per cent. The Kahn reaction was doubtful, but the Wassermann reaction was negative. Urinalysis revealed a specific gravity of 1.014; albumin, 4 plus; Bence Jones protein, positive. Nonprotein nitrogen varied from 76 to 144 mg. per cent; creatinine, from 7 to 12 mg. per cent; calcium, from 9.2 to 9.7 mg. per cent; phosphorus, 6.9 to 7.1 mg. per cent; total protein, 7.2 gm. per cent, with albumin-globulin ratio, 3.3 to 3.9.

On examination of the marrow, masses of myeloma cells were observed. The cells were for the most part large and discrete. There were almost no normal marrow elements.

Roentgenograms of the skull showed multiple radiolucent areas.

Comment: This patient presented himself because of a swelling of the jaw. Examination revealed a mandibular mass which was found on biopsy to be a myeloma. Subsequently he was observed to have a disseminated form of the disease.

Case 13. Splenomegaly. A Negro female, aged 53, entered the hospital on July 24, 1952, with a cerebral concussion following an automobile accident. At this time enlargement of the liver and spleen was noted and a rectus muscle contusion was reported. The patient had lost from 20 to 50 pounds during the last year.

The blood pressure was 165/100 mm. of Hg; pulse, 100; temperature, 98.2° F.; respirations, 28. There were a few petechiae and hemorrhages over the chest. The liver was 6 cm. below the costal margin. The spleen filled the entire left upper quadrant and extended 14 cm. below the costal arch. The extremities showed a trace of edema but no adenopathy.

Analysis of the blood showed: hemoglobin, 8.5 gm. (55 per cent); red blood cells, 3.23 million; white blood cells, 7,000; the Kahn reaction was negative. Nonprotein nitrogen was 20 mg. per cent; total proteins, 5.8 gm. per cent; albumin-globulin ratio, 3.5/2.3.

A roentgenogram revealed an increase in the cardiac shadow.

On September 25 the blood count was as follows: hemoglobin, 8.1 gm. (52 per cent); red blood cells, 2.74 million; white blood cells, 13,400; polymorphonuclear leukocytes, 32 per cent; bands, 1 per cent; lymphocytes, 29 per cent; monocytes, 3 per cent; eosinophils, 2 per cent; plasma cells, 33 per cent; nucleated red cells, 1 per 100 leukocytes. The platelets appeared decreased. On September 30 the white blood cells had risen to 49,500, and the plasma cells were 53 per cent.

On October 3 a transfusion was given.

On October 9 the hemoglobin was 7.6 gm. (49 per cent); white blood cells, 49,900; polymorphonuclear leukocytes, 18 per cent; lymphocytes, 13 per cent; monocytes, 2 per cent; plasma cells, 67 per cent; nucleated red blood cells, 1 per 100 leukocytes.

On October 10 the blood pressure was 150/100 mm. of Hg. The patient appeared pale and chronically ill. Râles were heard in the right base. The ankles were edematous. Specific gravity of the urine was 1.020; albumin, 4 plus; Bence Jones protein still negative; total protein, 6.2 gm. per cent; albumin, 4.6; globulin, 1.6; phosphorus, 4.3 mg. per cent; alkaline phosphatase, 1.5 Bodansky units.

There was questionable pleural effusion. Roentgenographic survey of the skull and pelvis was unrevealing. Mantoux reaction was positive, 1:1,000. The marrow report on October 28 read: "No spicules were obtained on sternal aspiration." Splenic biopsy revealed homogeneous sheets of plasma cells.

Pericardial effusion was demonstrated on October 29, and a transfusion was

given on November 1, at which time the urine was still negative for Bence Jones protein.

Death occurred on November 6, 1952.

A diagnosis of splenic multiple myeloma with hemorrhagic pericardial effusion was corroborated at autopsy.

Comment: Multiple myeloma manifested itself in this case by splenomegaly and changes in the peripheral blood. There were no significant chemical or roentgenologic changes. The marrow was not diagnostic, but splenic biopsy substantiated the subsequently proved myeloma. At autopsy osteofibrosis of the marrow with areas of myeloma was found.

This case was unique in our series in that all the other cases could be diagnosed with certainty on the basis of the marrow examination.

Case 14. Constipation. A Negro male, aged 49, gave a history of constipation of one year's duration, blood in the stools for six months, indigestion for one and one-half years, cramps in the legs, and weakness and anorexia for six months, during which period there was weight loss of 20 to 25 pounds. Pallor and dullness and decreased breath sounds in the base of the right lung were observed.

A roentgenogram revealed an osteolytic lesion of the fourth rib.

Nonprotein nitrogen was 33 mg. per cent; total protein, 6.2 gm. per cent; hemoglobin, 3.1 gm. (20 per cent); red blood cells, 1.29 million; white blood cells, 1,700; polymorphonuclear leukocytes, 69 per cent; bands, 11 per cent; lymphocytes, 19 per cent; monocytes, 1 per cent. Platelets were diminished. Urinalysis showed 4 plus albumin but was negative for Bence Jones protein.

The marrow was replaced by plasma cells, which frequently occurred in large clusters and which numbered many young ones.

The autopsy report read in part: "Diffuse myeloma, chronic interstitial nephritis, chronic fibrosing tuberculosis of both upper lobes, focal hemorrhagic bronchopneumonia."

Comment: The symptoms suggested carcinoma of the terminal colon. The absence of anemia due to iron deficiency and the presence of severe leukopenia suggested the existence of a lesion replacing the marrow, which was found to be multiple myeloma on marrow examination.

Case 15. Hydrothorax. A white male, aged 51, entered the Cook County Hospital on November 9, 1952. He reported the onset of an upper respiratory infection with a nonproductive cough five weeks previous to admission. Before entering the hospital the patient had been hospitalized elsewhere, but the diagnosis was not available. A thoracentesis of the left side yielded an "orange" colored fluid. The patient had lost 25 pounds in the preceding month. Questioning did not reveal hemoptysis, night sweats or thoracic pain.

The patient was pale and appeared moderately ill. The blood pressure was 110/70 mm. of Hg; pulse, 84; respirations, 22. There were moderate signs of cervical venous distention. Examination of the lungs revealed fluid occupying all but the apex of the left chest cavity, a finding confirmed roentgenographically. The liver was displaced 4 to 5 cm. downward. The right lung field was entirely clear, and the heart was displaced to the right by the pleural effusion of the left.

Blood findings on admission were: red blood cells, 2.36 million; hemoglobin, 7.0 gm. (45 per cent); white blood cells, 6,750; platelets, increased in number; polymorphonuclear leukocytes, 40 per cent; bands, 8 per cent; eosinophils, 5 per cent; lymphocytes, 34 per cent; monocytes, 13 per cent.

Because the patient had an unexplained anemia a marrow examination was made. This revealed 70 to 80 per cent replacement of the marrow by plasma cells, most of which were mature, although some younger forms were present. Many plasma cells were binucleated and appeared in syncytium. The marrow observations were interpreted as being compatible with multiple myeloma.

On January 19 urinalysis was positive for Bence Jones protein, although the specimen on admission was negative. Total protein was 9.6 gm., with the albumin-globulin ratio, 2.4/7.2; alkaline phosphatase, 2.1 Bodansky units; nonprotein nitrogen, 27 mg. per cent; cholesterol, 85 mg. per cent. The electrocardiogram was not remarkable.

Numerous thoracenteses yielded amounts varying from 250 c.c. to 3,500 c.c. Bronchoscopy revealed only that the left bronchus was displaced medially, with increased secretions coming from the base of the orifice. The tuberculin reaction was negative. The pleural fluid changed in character: at first clear, then serosanguineous, then brownish green, foul smelling and thick, and, finally, somewhat thinner, but grossly purulent.

Open drainage had not been instituted when empyema was first recognized because of the diagnosis of multiple myeloma.

Serial roentgenograms of the chest indicated that rapid effusion followed each removal of fluid. One culture was positive for hemolytic streptococcus of the alpha type. A lateral roentgenogram of the lumbar spine was essentially normal. The right lung remained clear. The last roentgenogram indicated a moderate amount of pleural thickening and only partial reëxpansion of the left lung.

Comment: There was nothing in the patient's history and nothing in the physical signs or symptoms on examination to suggest multiple myeloma. The unexplained anemia led to a search for etiologic factors. It was then that examination of the marrow revealed the diagnosis. This was subsequently substantiated by the finding of Bence Jones proteinuria and hyperglobulinemia. The relation of the hydrothorax to the multiple myeloma remains unelucidated.

Summary Review of Total Series

Sex and Age: Of the 75 cases in our series, 31 were women and 44 men. The ages ranged from 36 to 79 years, but in 85 per cent of the cases, the ages ranged from 50 to 70 years.

Physical Signs and Symptoms: Physical signs and symptoms in the series were almost exclusively associated with concomitant diseases. Nine patients had visible masses, seen mostly over the skull, the ribs and the jaw. Most patients were pale and appeared chronically ill. Virtually all patients had nonspecific symptoms, such as weakness, loss of weight and anorexia, epistaxes or rectal bleeding. Forty-seven had symptoms of bone pain, most frequently affecting the lumbosacral spine. Other areas affected were the thoracic and cervical vertebrae, the hips, rib cage and shoulders. Bone tenderness on examination was reported in 26 cases, in one of whom there had been an acute episode of back pain with inability to move the legs or to void for 10 hours. A previous admission had been for back pain, diagnosed as arthritis of the spine. It was only after laminectomy that the nature of

the disease became apparent. Two others were unable to walk or to move their legs.

Even though multiple myeloma was not originally considered in the group disclosed by roentgenologic evidence, it was pain that prompted the roentgenographic examination; hence, pain is important in symptomatology, as roentgenography is in diagnosis.

Three patients were entirely symptom-free. Two of these had been hospitalized because of unexplained anemia found on routine examination, and one was found to have an unexplained 4 plus albuminuria.

Laboratory Results: Hematology. The over-all hematologic data were as follows: In 80 per cent of the cases there was at least moderate anemia: a hemoglobin less than 10.9 gm. (70 per cent) and a red cell count less than 3.50 million. Fifty per cent of the patients had a moderately severe anemia: hemoglobin of less than 7.8 gm. (50 per cent), and a red cell count less than 2.50 million. There appeared to be no relationship between the severity of anemia and leukopenia. Few patients were leukopenic; the greatest number were within normal range; a few showed leukocytosis. Those who were leukopenic, however, showed a decrease in platelets as well.

One patient who was comatose on admission was found to have plasma cell leukemia. The white blood cell count was 69,000. The presence of 64 per cent plasma cells in the peripheral blood film clarified the problem. In three other cases plasma cells were found in the peripheral smear and prompted further investigation. In four cases there were nucleated red blood cells in the peripheral smear, and in one a leukemoid reaction was seen. Because of the extensive marrow involvement, one wonders why nucleated red blood cells and leukemoid reactions are not seen more frequently. Rouleau formation was seldom reported but was seen in most films which were reviewed. A macrocytosis was seen in three cases which suggested pernicious anemia. In two of these patients, a smooth tongue had also been noted.

Urinalyses. The urinary examinations were of interest because 80 per cent of the patients had between 1 and 4 plus albuminuria; however, only 23 per cent showed a Bence Jones protein reaction. Bence Jones protein was not found in any case without albuminuria. The low percentage of Bence Jones protein in our series as compared with others was probably due to failure to make more than one or two determinations.

Marrow Study. Of all the laboratory tests, by far the most important and significant is an examination of the marrow. In 66 patients the marrow was diagnostic of multiple myeloma. In six cases in which the marrow was not examined, postmortem examination revealed multiple myeloma. In two cases, it was the biopsies of soft tissue swellings over the bones that revealed multiple myeloma; hence, the marrow actually was diagnostic in all but one case (case 13) in which it was examined. Usually the marrow was abundantly cellular and to the extent of from one third to almost completely replaced by plasma cells.

Biochemical Determinations. The reversed albumin-globulin ratio with hyperglobulinemia and the elevated levels of calcium, alkaline phosphatase and nonprotein nitrogen have been the most valuable of all biochemical determinations.

A reversed albumin-globulin ratio with hyperglobulinemia was found in 37 of 60 cases examined. The highest range of globulin was 11.8 gm. per cent. In 10 cases it was the discovery of a reversed albumin-globulin ratio that was the first clue suggestive of multiple myeloma, notwithstanding the fact that determination of the albumin-globulin ratio is not a routine procedure. In two cases it was the presence of jaundice, and in three, the presence of a palpable liver which motivated investigation of liver function. In the remaining cases a total protein determination and the albumin-globulin ratio were obtained in order to evaluate the general nutritional status.

Elevated calcium above 11 mg. per cent was seen in 17 of 33 cases. The highest value was 18.4 mg. per cent, seen in two cases. The greatest number, however, were in the range from 11 mg. to 14 mg. per cent.

Alkaline phosphatase was elevated in 12 of 43 cases. In most cases the elevation was only slightly above normal. This is to be expected, inasmuch as the lesions are not osteoblastic.

Nonprotein nitrogen of 40 mg. per cent or higher was found in 50 per cent of the patients examined. Many of these died in uremia.

Roentgenologic Survey. Of prime importance as a diagnostic aid is the roentgenographic examination of the skeletal system, mainly the skull, pelvis, vertebrae and ribs. Osteolytic lesions were found in 67 of 75 cases. Six showed no roentgenologic evidence and two were not examined. Most commonly the lesions are seen as osteolytic or punched-out areas, with little or no surrounding osteoblastic activity. This is particularly true of the flat bones, such as the skull and pelvis, but any combination may be seen, such as osteoporosis and osteolytic lesions, sharply circumscribed lesions, poorly circumscribed lesions simulating metastatic lesions, and severe bone destruction resulting in paper-thin cortex or, occasionally, no cortex at all. New bone formation is unusual but is seen on rare occasions.

Conclusions

Clinical diagnosis alone can suggest but cannot establish the existence of multiple myeloma. Evidence cannot be had without laboratory tests. Roentgenologic survey, Bence Jones proteinuria and serum globulin determinations are diagnostic aids. Bone lesions, Bence Jones proteinuria, an increased serum globulin—these are not unfailingly present together or even separately. It is the examination of the marrow, however, which is diagnostically of greatest import, for it alone can unmistakably establish the presence of multiple myeloma when the marrow is observed to be replaced by plasma cells. This is not a plea for routine or unmotivated marrow ex-

amination. The best diagnostic guidepost against being misled remains an acute awareness that "everything is not what it seems," that the implications of vague and equivocal presenting symptoms must be explored fully, for they may indeed be the clues, however capricious, to the diagnosis of multiple myeloma.

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THROMBOCYTOPENIA AND ABNORMAL BLEEDING IN MULTIPLE MYELOMA *

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DURING the course of multiple myeloma most patients exhibit a tendency to bleed. Although it may be an early manifestation, the incidence of abnormal bleeding is greater in the more advanced phases. The severity of bleeding varies from petechiae to exsanguination.[1] Despite wide recognition of this feature of myeloma, its pathogenesis has remained obscure. The etiologic factors most often suggested have been (1) the presence of abnormal plasma proteins impairing normal coagulation,[2, 3, 4, 5] and (2) deficient clot retraction, of unstated cause.[2, 3] That the platelet count in myeloma is usually normal has been repeatedly stated by Custer,[6] Limarzi,[7] Bayrd and Heck [8] and others.[7, 8, 9]

One would expect a megakaryocytopenia in a disease characterized by anemia of the myelophthisic variety. It has been our experience that the megakaryocytes in the marrow smears of myeloma patients are consistently diminished, usually to a rather marked degree. Furthermore, a significant number of these patients manifest impaired granulocytopoiesis as well as anemia and megakaryocytopenia. The myelophthisis occasionally is of a degree making the clinical picture indistinguishable from aplastic anemia.[1, 10, 11]

Since deficient clot retraction has been a common observation in myeloma, the investigation of the incidence of thrombocytopenia would be logical. Because marrow megakaryocytopenia has been consistently found in our cases, a study was undertaken to review the occurrence of thrombocytopenia in a series of 58 histologically proved cases of multiple myeloma. These findings are correlated with the bleeding episodes observed in these cases.

METHODS

All the platelet counts in our patients were performed by the same technician. Counts were made from cutaneous blood, using the Rees-Ecker method. A comprehensive review by Aggeler, Howard and Lucia [12] using this method of counting stated that the critical level of platelets varied in primary and secondary thrombocytopenia, being 190,000/cu. mm. in the former and 230,000/cu. mm. in the latter. Within the range of 30,000 to 190,000, however, they found no significant correlation between the level of the platelet count and the severity of the bleeding.

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The experience in our hemocytologic laboratory has shown that the range of normal platelet count is 200,000 to 400,000/cu. mm. This is the range expressed as normal for the Rees-Ecker method on cutaneous blood by most observers using this technic.[6] It has been uncommon in our experience to encounter bleeding due to thrombocytopenia with platelet counts of over 170,000/cu. mm.

The diagnosis of multiple myeloma was established in all the cases in our series by the demonstration of myeloma cells in the marrow, by either sternal aspiration, sternal biopsy or necropsy.

Results

In the series of 58 cases of myeloma, platelet counts were done in 31. More than two thirds of these patients had platelet counts below 170,000/cu. mm. (figure 1). All but two of the remaining nine had counts of less than 250,000.

Of the 15 patients of the total series exhibiting major bleeding episodes, nine had platelet counts (figure 1). Eight of the nine had distinctly low counts. The ninth patient bled for causes to be discussed later. The sites of abnormal bleeding in these patients were (as noted by others [2, 3, 4, 5]) principally the nose and the gums. One patient, in whom a platelet count was not obtained, became exsanguinated from epistaxis. Postmortem examina-

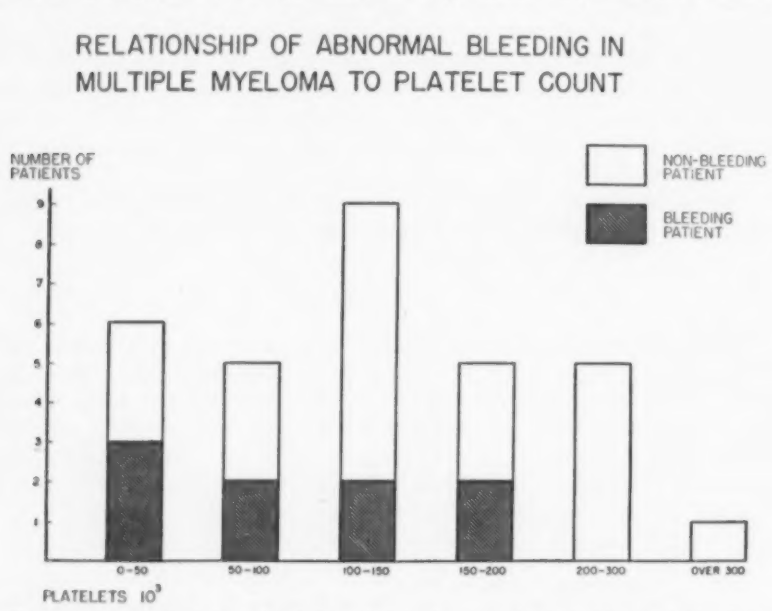

Fig. 1. Graphic depiction of relation of thrombocytopenia to incidence of bleeding.

tion revealed an aplastic marrow with virtually no megakaryocytes, making peripheral thrombocytopenia probable.

Following are brief protocols of proved cases of multiple myeloma demonstrating the close relationship of bleeding and thrombocytopenia.

Case Reports

Case 1. A 45 year old colored male presented as the chief clinical feature, massive hematuria without preceding signs or symptoms of myeloma. His hemogram, of both peripheral blood and marrow, suggested the diagnosis of acute aplastic anemia. The platelet count was 36,000/cu. mm. Hyperglobulinemia was not observed.

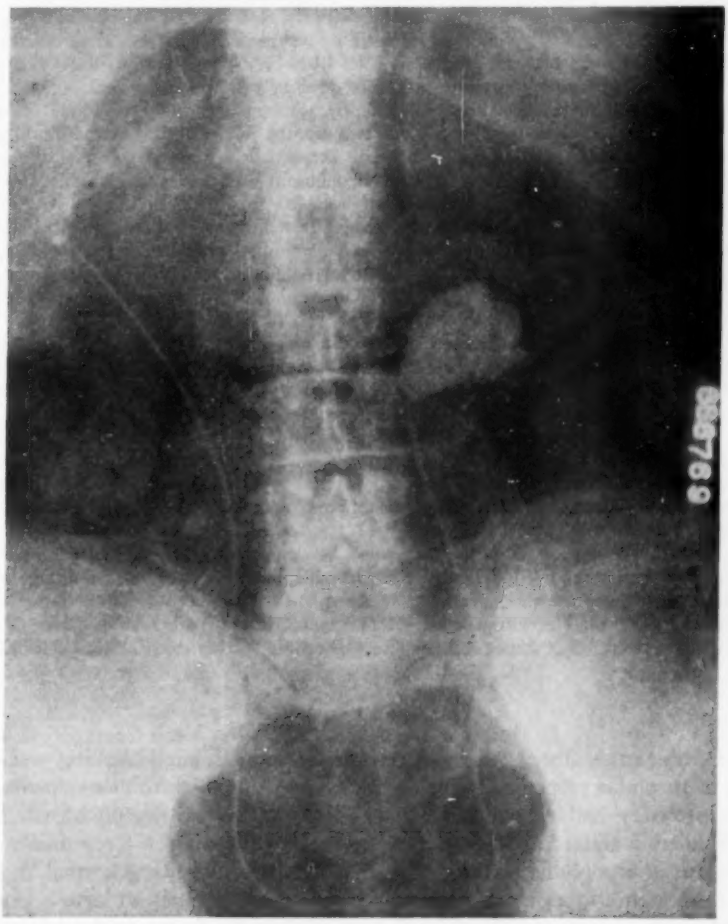

Fig. 2. Retrograde pyelograms demonstrating a large staghorn calculus in the left renal pelvis (case 3).

Case 2. A 72 year old white woman previously had been treated elsewhere as myelophthisic anemia. On her second visit to our clinic she demonstrated extensive generalized ecchymoses, some of which assumed proportions of large hematomas. The platelet count was found to be 16,000/cu. mm.

Case 3. A 58 year old white man was admitted with pneumonia and a past history of hematuria. Routine blood examination revealed a severe anemia which on investigation proved to be due to multiple myeloma. Platelet count at that time was 112,000/cu. mm. He was shown to have a large staghorn calculus in the left renal pelvis (figure 2). Following cystoscopy he bled almost uncontrollably. Successive platelet counts two days apart were 54,000 and 24,000/cu. mm.

Case 4. A 65 year old white woman with multiple myeloma presented a two weeks' history of expectorating red clotted blood and vomiting blood as well. Although postmenopausal by more than a decade, she had noticed vaginal bleeding off and on for two months. Pelvic examination revealed no local abnormality. Serial platelet counts demonstrated a progressive fall from 120,000/cu. mm. to 40,000/cu. mm.

Case 5. A 54 year old white man bled profusely following a dental extraction. Transfusion was made exceedingly difficult by autohemagglutination, which obviated accurate typing and cross-matching. For two months following the extraction he continued to bleed despite all efforts to provide hemostasis. Platelet count at the onset of bleeding was 88,000/cu. mm. The blood albumin was 2.46 and globulin 9.00 gm. per cent. Hemoglobin shortly before death was 2.0 gm.

Case 6. A 64 year old white man gave a past history of duodenal ulcer and of familial telangiectasia. Although he had had occasional nose bleeds most of his life, the epistaxis became severe three months prior to admission. During this period he had also noticed dark blood in his stools. On admission a fresh hemorrhage was detected in the right retina. The platelet count was 108,000/cu. mm.

Case 7. A 60 year old white man noted a single tarry stool prior to the admission in which myeloma was diagnosed. Serial platelet counts remained approximately 80,000/cu. mm. He experienced no further bleeding for six weeks but then developed extensive generalized ecchymoses and died shortly thereafter.

Case 8. A 61 year old colored man was admitted because of massive rectal bleeding and severe epistaxis. The high viscosity of blood obtained for routine examination raised the suspicion of cryoglobulinemia. Sternal aspiration established the diagnosis of multiple myeloma. Platelet count was 154,000/cu. mm. The blood albumin was 2.88 and globulin 6.91 gm. per cent.

Case 9. A 49 year old white man was also suspected of having multiple myeloma when technicians reported difficulty counting his blood because of clumping and a syrupy consistency of the specimen. Subsequent studies proved the diagnosis of myeloma. The platelet count was 190,000/cu.mm. He had severe epistaxis and bled profusely from his sternal biopsy site. Bleeding in this case is discussed below.

General Comment

Of nine cases abstracted above, the first seven exhibited bleeding probably due to thrombocytopenia. The eighth case exhibited thrombocytopenia but also probably had cryoglobulinemia. The ninth case demonstrated cryoglobulinemia and a low normal platelet count. Bleeding is a common manifestation of cryoglobulinemia, all other clotting factors being normal.[13, 14]

Although a myeloma patient who bleeds is more likely to have a platelet count made, one is impressed by the fact that none of our myeloma patients with normal platelet counts exhibited abnormal bleeding. Conversely, eight

of the nine who bled and who had platelet counts demonstrated remarkable thrombocytopenia.

Discussion

There is a lag between impaired thrombocytopoiesis and the development of peripheral thrombocytopenia, just as there is a lag between impaired erythrocytopoiesis and peripheral anemia. Accordingly, the consistent finding of megakaryocytopenia in examination of the marrow of myeloma patients in our clinic would predict subsequent peripheral thrombocytopenia almost as consistently. In all our marrow smears exhibiting myeloma cells there has been some megakaryocytopenia, usually of moderate to severe proportions, so that we consider this to have an incidence of 100 per cent in the series of 58 cases. The incidence of peripheral thrombocytopenia was 71 per cent (22 of 31 patients who had platelet counts). We believe this incidence reflects approximately what would be found if platelet counts were made on all myeloma patients.

The presence of a single normal platelet count does not exclude deficiency of this clotting factor as a cause of bleeding. It is likely that a patient may regenerate enough platelets to meet normal requirements but not possess regenerative reserve sufficient to cope with greater need. Thus epistaxis may become a hemorrhagic crisis in a patient with megakaryocytopenia. The level of megakaryocytes in the marrow is the best index presently available to judge platelet regenerative reserve.

Although we consider thrombocytopenia a common finding in multiple myeloma, it may not be the only factor causing bleeding in these patients. The presence of abnormal proteins in the circulation undoubtedly contributes to the bleeding tendency in multiple myeloma. Of these proteins the most culpable seems to be the group referred to as cryoglobulins. Cryoglobulins are probably not a specific protein, since extensive analyses by different observers [15, 16, 17] are not in exact agreement. Their significant common characteristic is the thickening of blood cooled to a few degrees below body temperature. Such thickening may so impair blood flow in small vessels that the resulting ischemia leads to gangrene, much as in Raynaud's disease. This pseudo-clotting readily dissolves upon warming to body temperature, inducing brisk bleeding from the gangrenous vessels. Such bleeding is a particularly acute hazard in cryoglobulinemic patients who undergo surgery. This presents an interesting paradox. Venipuncture is extremely difficult because the blood "clots" so rapidly, yet such patients subjected to operation exhibit uncontrollable bleeding.

Extramedullary lesions are present in the majority of autopsied cases of multiple myeloma.[18] The reticuloendothelial system, especially the liver, is involved most often. This logically leads to the speculation by Limarzi [2] that hypoprothrombinemia may contribute to the cause of bleeding in myeloma. Similarly, fibrinogenopenia may also contribute to the problem, as in two cases reported by Waldenstrom.[19]

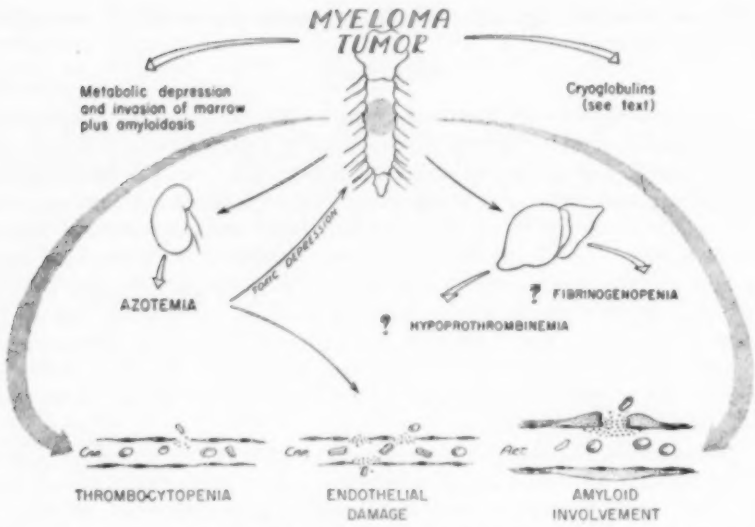

FIG. 3. Summary of hypothetic mechanism by which bleeding can occur in multiple myeloma.

Two other mechanisms are often cited in the explanation of bleeding in myeloma. The first of these evolves from the similarity and frequent coexistence of amyloidosis and myeloma,[9] emphasizing the involvement of blood vessel walls directly by infiltrating amyloid material.[20] The second is the uremia resulting from extensive renal impairment in myeloma. The mechanism of bleeding here is toxic damage to the endothelium of the smaller vessels, plus further toxic depression of thrombocytopoiesis.

A summary of hypotheses regarding the bleeding in myeloma is presented in figure 3.

CONCLUSIONS

1. Megakaryocytopenia is consistently present in the marrow of patients with multiple myeloma.

2. Thrombocytopenia occurs in the majority of patients with multiple myeloma.

3. Thrombocytopenia is a major cause of abnormal bleeding in myeloma patients.

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THE FAILURE OF HYPERTONIC SALINE IN THE TREATMENT OF HYPONATREMIA AND EDEMA IN CONGESTIVE HEART FAILURE*

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THE appearance of hyponatremia and edema in a patient with congestive heart failure represents a serious disturbance of electrolyte equilibrium. This disorder may develop quite insidiously or it may be acute in onset. The latter state, often referred to as the low salt syndrome, is accompanied in the majority of cases by mental aberrations, anorexia, nausea, vomiting, abdominal cramps, nitrogen retention and usually peripheral vascular collapse. On the other hand, chronic dilution hyponatremia is not associated with the usual signs and symptoms observed in patients with the acute depletion syndrome.[1] The exact mechanism that leads to the production of a state of dilution hyponatremia is not clearly understood. It has been related to alterations in cellular osmolarity. Cellular failure may develop due to inactivation of intracellular base.[2] Unfortunately, these patients cannot respond to this altered electrolyte state by excreting more salt, for the primary renal mechanism in play in patients with congestive failure prevents this. The remaining alternative is to retain water, which invariably leads to edema. Primary water retention may then be intensified by the sustained production of antidiuretic hormone.[3]

During the course of the past two years we have had the opportunity to observe several patients who presented the picture of hyponatremia and edema in congestive heart failure. In all but two instances the clinical picture developed rapidly following intensive mercurial therapy. It was readily apparent that any attempt to establish normal tonicity must involve the infusion of various amounts of hypertonic saline, in order to prevent further expansion of the extracellular space. In most instances deficits were calculated on the basis of total body water, as suggested by Peters.[4] Seven cases are presented which clearly illustrate that any attempt at correction of this abnormality is not only fruitless, but may lead to the aggravation of the patient's clinical state.

CASE REPORTS

Case 1. A 61 year old white female was admitted to the hospital on January 14, 1953, because of abdominal pain and dyspnea of three weeks' duration. She was known to have rheumatic heart disease and had been treated for congestive failure for a number of years. Therapy consisted of digitalis, low salt diet, and periodic

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mercurial diuretics. On entry, temperature was 98.6° F.; pulse, 110 (irregular); respirations, 20. She appeared to be in moderate respiratory distress. Positive findings on examination included icteric sclerae, dry tongue, malar flush, distended neck veins and basal râles. The heart was enlarged, with an irregular rhythm and a grade 3 apical systolic and diastolic murmur. The liver was enlarged and tender. There was edema of the extremities. *Course:* The patient was given oxygen, more digitalis and ammonium chloride, and was placed on a low salt diet. She failed to respond to treatment. Thiomerin was administered, without effect on the edema fluid, and the patient became more drowsy and apathetic. On January 20 serum Na was reported as 123 mEq./L.; Cl, 87 mEq./L. All the other chemistries were within normal limits except for the presence of slight elevation of the blood urea nitrogen. The patient was treated vigorously with 5 per cent saline with drastic restriction of total fluid intake to less than 1,000 c.c. On January 22 the serum Na was 131 mEq./L. and remained close to that on succeeding determinations. The patient showed no clinical improvement, but in fact continued to gain weight. There was no diuresis. She died in coma on January 30.

Case 2. A 56 year old white female was treated for a myocardial infarction in February, 1952. Since then she had been on digitalis, low salt diet and periodic diuretics. She entered the hospital on December 1, 1952 because of shortness of breath and chest pain of recent onset. On examination, temperature was 99° F.; pulse, 100; respiration, 24; blood pressure, 140/80 mm. of Hg. There was some distention of the neck veins. Râles were heard at both lung bases. The heart was enlarged to the left by percussion, and there was a grade 1 apical systolic murmur. Electrocardiogram showed left ventricular strain. *Course:* The patient was placed on a strict cardiac regimen and given mercurial diuretics. On December 6 increased shortness of breath was noted and the patient appeared lethargic. Urinary output had fallen to less than 650 c.c. On December 8 edema was noted in the extremities and the dependent portions of the body. Chemistries were obtained. Serum Na was 124 mEq./L.; Cl, 84 mEq./L.; K, 5.2 mEq./L.; and CO_2 18 mEq./L. The patient was treated vigorously with hypertonic saline, but serial electrolyte determinations during the next few days continued to reveal evidence of hyponatremia. Furthermore, it was not possible, as is often the case, to restrict her fluid intake sufficiently. Oliguria persisted, and on the day prior to death the serum Na was 129 mEq./L.; Cl, 94 mEq./L.; blood urea nitrogen, 90 mg. per cent; CO_2, 17 mEq./L. The patient lapsed into coma and died suddenly on December 14. Her clinical course during the last five days of her illness is summarized in figure 2.

Case 3. A 52 year old white female was admitted to the hospital on September 18, 1952, because of progressive swelling of the lower extremities of several months' duration. Dyspnea and anorexia had developed more recently. She had been treated at another hospital recently with periodic injections of mercurials. On examination, temperature was 98° F.; pulse, 152; respiration, 20; blood pressure, 114/90 mm. of Hg. There was marked distention of the neck veins. Râles were audible at both lung bases. The heart was enlarged on percussion to the anterior line. The liver was felt two fingerbreadths below the right costal margin. Marked pitting edema of the lower extremities and dependent portions of the trunk was present. *Course:* The patient was placed on the usual cardiac regimen, including injections of mercurial diuretics as needed. On September 19 the following chemistries were reported: blood urea nitrogen, 29 mg. per cent; Na, 140 mEq./L.; Cl, 97 mEq./L.; K, 4.4 mEq./L.; CO_2, 24 mEq./L. The response to therapy was poor, and the patient became weaker and apathetic. The urinary output was less than 750 c.c. per day. On October 4 a serum Na was 123 mEq./L.; Cl, 96 mEq./L.; and CO_2, 17 mEq./L. The patient became sluggish and more edematous. Subsequent serial Na determinations continued to reveal evidence of hyponatremia. The patient was treated vigorously with 5 per

cent saline and finally, on October 13, a Na determination was 131 mEq./L. and a Cl was 97 mEq./L. Despite the return of the electrolytes to near normal concentration, the patient pursued a downward course and became more edematous. Following each injection of the hypertonic saline she became extremely thirsty. On October 16 she finally lapsed into coma and died shortly after. Autopsy was obtained and showed idiopathic cardiac hypertrophy, probably beriberi heart disease.

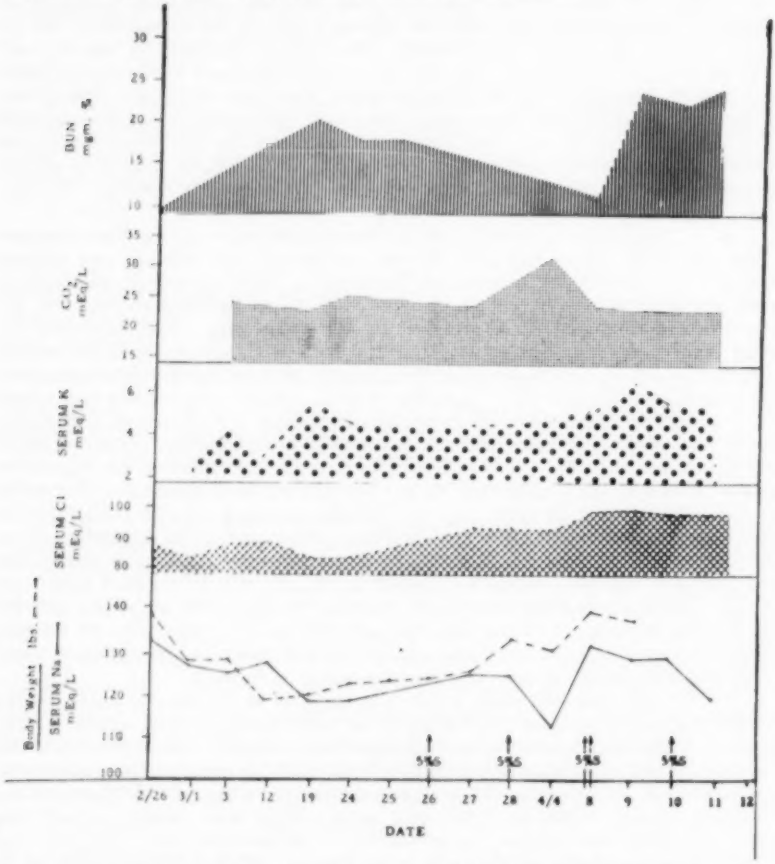

FIG. 1. Response of case 4 to hypertonic saline. Administration of hypertonic saline failed to restore tonicity or to initiate a diuresis.

Case 4. A 30 year old white male had had known rheumatic heart disease since the year 1948. He had been on digitoxin since that time, in addition to a low salt diet and mercurial diuretics at intervals. He entered the hospital on February 25, 1952, with a five month history of ankle edema, shortness of breath and fatigue. On admission, temperature was 99° F.; pulse, 56; respirations, 28; blood pressure, 118/85 mm. of Hg. Positive findings included dullness to percussion and râles at the right base, cardiac enlargement with an apical systolic and diastolic murmur, hepatomegaly

and ankle edema. An electrocardiogram revealed right ventricular enlargement, and chest plate showed congestive changes. *Course:* He was placed on a strict cardiac regimen, including injections of mercurials. Initially he had a good response to therapy. Subsequently he developed mercurial fastness, and serial serum Na determinations revealed persistent hyponatremia. Hypertonic saline was given and in-

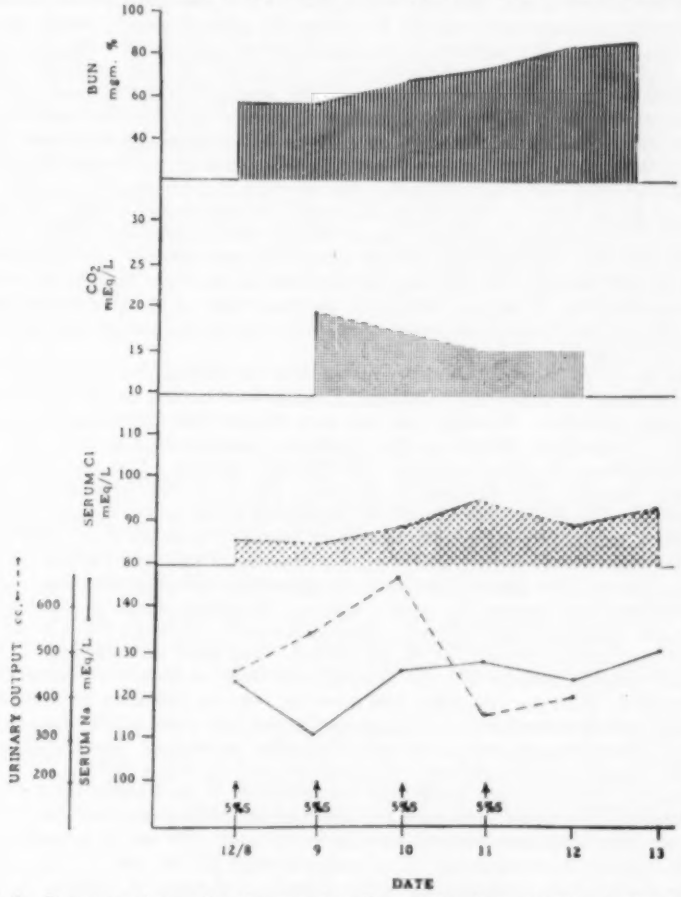

FIG. 2. Response of case 2 to hypertonic saline. Oliguria persisted and the patient died 17 days after entry into the hospital.

duced marked thirst. The patient's constant pleas for water were answered by members of his immediate family. On April 4 the serum Na was 116 mEq./L. and serum Cl 93 mEq./L., and he had become more edematous. On April 7 the patient was isolated and a more vigorous attempt to correct the electrolyte imbalance was made. Over a two day period a total of 750 c.c. of 5 per cent saline was given and fluid intake was restricted to less than 1,000 c.c. On April 8 serum Na was 134 mEq./L. No diuresis resulted, and he continued to gain weight and died seven days later.

Postmortem examination revealed rheumatic heart disease with mitral stenosis. This patient's course is summarized in figure 1.

Case 5. This female patient was admitted to the hospital on December 16, 1952, because of profuse edema of the lower extremities and abdominal swelling associated with evidence of right and left ventricular failure. She was known to have atherosclerotic heart disease, and had been on digitalis and a low salt diet for about one year. On entry, temperature was 98° F.; pulse, 90; respirations, 28; blood pressure, 120/80 mm. of Hg. She appeared to be acutely and chronically ill. She was apprehensive and confused. The neck veins were distended. A few scattered wheezes were heard in the lungs. The heart was greatly enlarged to the left, with a totally irregular rhythm and a grade 2 apical systolic murmur. The abdomen was distended and there was 4 plus pitting edema of the extremities. *Course:* On December 17 the following laboratory determinations were reported: blood urea nitrogen 35 mg. per cent; Na, 124 mEq./L.; Cl, 71 mEq./L.; Co_2, 42 mEq./L.; protein, 6.7 gm. per cent; albumin, 5 gm. per cent. The patient was treated with the usual cardiac regimen, in addition to Pronestyl for control of frequent extrasystoles originating in the ventricle. Five per cent saline was given by vein to correct the hypotonicity. On December 19 the Na was 132 mEq./L.; Cl, 108 mEq./L.; K, 5.6 mEq./L.; CO_2, 19 mEq./L.; and the blood urea nitrogen, 42 mg. per cent. Despite the return of the chemistries to near normal the patient became massively edematous, extremely drowsy and finally unresponsive. She died on January 2, 1953.

Case 6. A 57 year old white female entered the hospital on January 29, 1953, because of bouts of paroxysmal nocturnal dyspnea and marked peripheral edema of many weeks' duration. Recently, she had been treated with digitalis and occasional injections of mercurial diuretics. On admission, temperature was 100° F.; pulse, 100; respirations, 36; blood pressure, 218/152 mm. of Hg. The neck veins were distended; no râles could be heard in the chest, but the patient was having shallow respirations. The heart was enlarged by percussion to the anterior axillary line and there was a grade 3 apical systolic murmur. The liver was felt five fingerbreadths below the right costal margin, and was very tender. There was marked peripheral edema. *Course:* The patient was treated vigorously with digitalis, low salt diet, aminophylline, and oxygen by nasal catheter. Mercurial diuretics were likewise given. On January 30 the following chemistries were reported: Na, 126 mEq./L.; Cl, 84 mEq./L.; CO_2, 24 mEq./L.; K, 3.8 mEq./L.; and blood urea nitrogen, 5 mg. per cent. The patient became cold and clammy, and signs of congestive failure became more marked. Five per cent saline was given by vein; on February 3 all the electrolytes were within normal limits. The patient lapsed into coma and died on February 4. At no time did a diuresis occur with diminution of edema. There was no effect from the infusion of the hypertonic salt except to produce severe thirst.

Case 7. A 68 year old white male was admitted to the hospital on February 7, 1953, because of dyspnea, orthopnea and ankle edema of three months' duration. He had never been adequately treated for this in the past. On entry, temperature was 101° F.; pulse, 76; respirations, 76; blood pressure, 120/90 mm. of Hg. Positive findings included the presence of aortic stenosis and signs of congestive failure. There was marked edema of the extremities. The patient responded nicely to the usual cardiac regimen; on February 17 he was noted to be dyspneic and lethargic. Chemistries were obtained and the serum Na was 120 mEq./L.; Cl, 88 mEq./L.; K, 6 mEq./L.; CO_2, 22 mEq./L. He was treated with 5 per cent saline with no effect and died shortly after.

Comment

Our experience would suggest that the infusion of hypertonic saline in the refractory patient with hyponatremia with edema serves little purpose.

In many patients it may have a deleterious and even harmful effect. We have observed the following patterns of reaction after this method of treatment: (1) A normal electrolyte concentration may be established with no effect on the edema and with no precipitation of diuresis. The patient pursues a downward course and dies in a short time. (2) Mercurial diuretics may be given following the correction of the hyponatremia with hypertonic salt solutions. A prompt diuresis will result in some cases. However, the immediate recurrence of hypotonicity with reappearance of edema indicates the futility of this form of management. The prognosis remains poor despite the apparent temporary improvement. (3) This represents the picture most often observed in attempts at correction of this syndrome with hypertonic salt solutions. The patient develops intolerable thirst during the period of fluid restriction and saline infusion. It appears in most instances before the serum electrolytes have returned to their normal concentration. The craving for water becomes so intense that many in desperation will plead for liquid and finally refuse to coöperate further in attempts at fluid restriction. The unfortunate result of this venture is that more salt has been given with expansion of the extracellular space as water is once more freely ingested. The patient in fact becomes more waterlogged and more saltlogged, and still shows evidence of hypotonicity.

It should be stated that one cannot always clearly differentiate between dilution hyponatremia and the low salt syndrome originally described by Schroeder.[5] This is especially true when the latter is associated with edema. The rôle of mercury is difficult to define in view of the fact that both groups, oftentimes patients with severe congestive heart failure, may receive intensive therapy with this diuretic. However, if one is able to demonstrate that the presence of hyponatremia and edema has developed gradually, without resort to significant mercurial injection, then the hypotonicity cannot be attributable to an acute depletion syndrome. Such was thought to be the case in patients 5 and 6.

Recently, Elkington [6] has carefully analyzed 11 cases with hyponatremia and edema with congestive failure treated with hypertonic solutions of sodium. The majority of patients succumbed within two weeks of the institution of therapy. One patient died in 52 days despite the development of an adequate diuresis and the establishment of normal tonicity. Our experience has proved similar in that in no instance was there a diuretic response following the administration of hypertonic saline; furthermore, this syndrome was invariably fatal within a few weeks. It would seem, then, that the present mode of treatment of hyponatremia and edema in the presence of congestive failure is inadequate.

Summary

1. An evaluation of the treatment of hyponatremia and edema in congestive failure with hypertonic saline is made in seven cases.

2. The following conclusions have been reached: (a) This method of treatment is ineffective and may prove harmful; (b) the period of fluid restriction during the course of the infusion of the hypertonic saline is unbearable for most patients; and (c) the syndrome is invariably fatal.

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CASE REPORTS

EMOTIONAL FACTORS IN SCLERODERMA: CASE HISTORY*

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IN recent years more and more evidence has accumulated that certain ills which beset mankind are diseases of adaptation. Thus the physiologic adjustments of the body to stress can miscarry, leading to pathologic processes. Scleroderma has long been described in the medical literature as a disorder of unknown etiology. It is now realized that this is one of the group of so-called collagen diseases, and probably can be included in the pathologic processes described as diseases of adaptation. As it was realized that the adrenal cortex played an important part in the body's general adaptation, it is not surprising that ACTH and cortisone have become popular therapeutic agents in the treatment of this group of diseases. Selye [1] and many others have described the stresses which elicit these pathologic responses in organisms, emphasizing that, among others, emotional stresses can play an important rôle. The rôle of psychogenic factors in Raynaud's phenomenon, often a component part of scleroderma clinically, has recently been summarized by Millet et al.[2a, b] Other manifestations, such as the joint involvement, may in certain stages closely resemble those of rheumatoid arthritis, a disease whose psychosomatic implications are becoming more widely recognized.[3, 4] As far as is known by the authors there has not been a case of scleroderma reported in the literature that was treated by cortisone and also treated psychologically at the same time. For this reason, and because it illustrates the rôle of emotional factors in scleroderma, the following report is presented.

CASE REPORT

This patient was a 35 year old white widowed teacher. She had been a patient of the Browne-McHardy Clinic intermittently since 1934, and steadily for the year and a half prior to her death on May 21, 1951. She was seen over this period because of rapidly progressing Raynaud's phenomena and scleroderma with an obvious emotional component.

Family History: The patient was the second youngest of four children, the only girl in a wealthy family of prominent social status. Both parents (but particularly the father) were extremely strict, rigid and authoritarian, and regulated the lives of the children even after they were grown. All of the children lived in the same neighborhood, and the father kept a close check on the routines of his family in a patriarchal and extremely domineering manner.

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Past History: Relatively little is known about the patient's early development except that she was considered a quiet, conforming child, raised in a Victorian manner where prettiness, daintiness and female dependency were all emphasized. She was overprotected and restricted. She exploited her social status and prettiness, adopting in a rather childishly pleasant manner an attitude of being a superior creature who should be loved, cared for and protected. She did well in school and imagined that she revolted against her family when going to college, although this college was in her home town. She called this her "wild period," but questioning revealed only an average number of dates, an occasional drink and an even rarer hand-holding episode. She later became interested in preschool education and did postgraduate work in that field.

Presenting Illness: The patient was first seen in 1934. Notes taken in the history at that time reveal that there was a "considerable degree of nervous tension manifested by a feeling of uneasiness, palpitations, difficulty in sleeping, fainting and

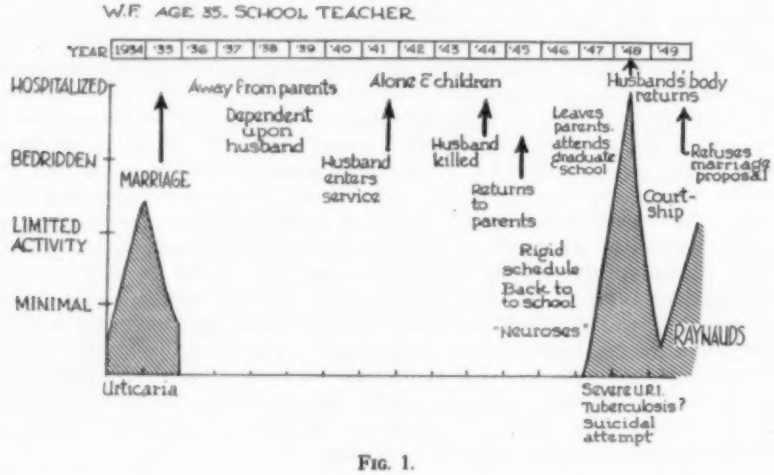

FIG. 1.

trembling." She was also treated for urticaria during this period. In 1935 she married a physician, moved away from home and, as far as is known, had no particular complaints. She considered this marriage an emancipation, with alleviation of much of the tension between herself and her family. She enjoyed the freedom of living an easy-going, carefree social life, with numerous servants to cater to her needs. A physician who knew the patient and her husband during this period stated that the latter was a rather passive individual whom she could dominate, and yet upon whom she depended almost completely. She adjusted poorly to her rôle as a doctor's wife in a small town, and looked down upon most of her acquaintances. In the main the relationship with her husband was fairly good and apparently sustained her, as judged by later events, though there was frequent conflict because of her jealousy over the normal demands of his practice. Her husband entered the military service in the early part of World War II and was killed in the latter part of 1944. At that time the patient stated she remained calm and composed "for the sake of the children."

After her husband's death, under pressure from her parents, not to mention financial insecurity and her own emotional dependency, she moved back to her home town in 1945. She became engrossed in a heavy schedule of studying and teaching.

She adopted a strict routine outlined by her father, "so strict that you could set your watch by my movements," and denied herself any chance for male companionship. Regarding the latter, she felt that "it would not be right and father would not approve." Any gaiety or levity made her feel quite guilty.

In 1948 her husband's body was returned from overseas. She reacted to this with extreme nervousness and depression, and coincidentally developed a chronic cough and fever which led to the discovery of pulmonary tuberculosis, which necessitated confinement in bed for four months. It is pertinent to note here that the patient, in describing this illness later on to the psychiatrist, never mentioned the fact that she had had tuberculosis. At some time during the same period she made a suicidal attempt. However, no particulars are available as to details or what precipitated it. She was extremely evasive and reluctant to talk about this episode, never mentioning it spontaneously. As far as is known, her family was never aware of this attempt and considered her a perfectly stable, mature individual.

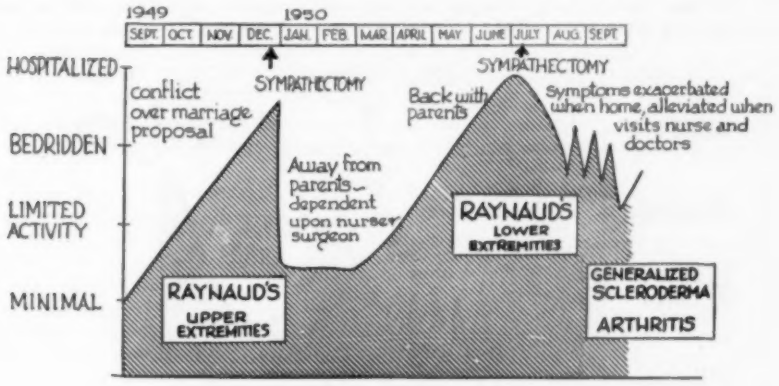

FIG. 2.

Following recovery from the tuberculosis the patient began seeing a physician of different racial background who lived in the same neighborhood. He became quite attentive, at times openly seductive, and frequently obtained admittance to her bedroom late at night under the guise of professional contact. For a short time she contemplated marrying this man, despite the fact that he was already married and had children. Finally, deciding that her father would not approve, she rejected this suitor in the latter part of 1949. At the same time there first appeared vasomotor phenomena manifested by pain, numbness, coldness and cyanosis of the hands. The diagnosis of Raynaud's phenomena was made. Unfortunately, her response to a medical regimen was poor. Because of extreme pain and cyanosis of the fingers and fear of gangrene, she was admitted to the hospital on December 26, 1949, for a two-stage bilateral upper dorsal sympathectomy.

In the hospital she was afraid to remain alone, and during this period she developed a very strong dependent attachment to one of her nurses, which remained the rest of her life. This, plus the encouragement and support of her physicians, seemed responsible for a temporary period of improvement. During the early months of 1950 she was depressed and preoccupied with such bodily changes as discoloration of her hands and feet, telangiectasia, periorbital edema and postoperative Horner's

syndrome. It was noted that she was quite narcissistic regarding her personal appearance.

During the next few months there was further progression of the disease, and because of the development of rather severe Raynaud's phenomena in the lower extremities she was re-admitted to the hospital in June, 1950, for lumbar sympathectomy. Despite surgical intervention, her symptoms relented only temporarily. She developed anorexia, loss of weight and occasional febrile episodes, and complained of beginning pain and stiffness in the knee joints. Minor electrocardiographic changes were noted. As her home was in a town some distance from the city in which her clinical treatment was carried out, she would visit her doctors on weekends in the company of the nurse-companion. It was noted repeatedly at this time that her somatic complaints were much alleviated when she left home to see the physicians and to visit friends. She often improved markedly within a few hours of stepping off the train and into the doctor's office. Furthermore, she was generally worse shortly after her return home. She required long hours of consultation, spending at least one hour each talking with her internist and surgeon. A half or full day of their time was often monopolized because of recurrent episodes of severe depression

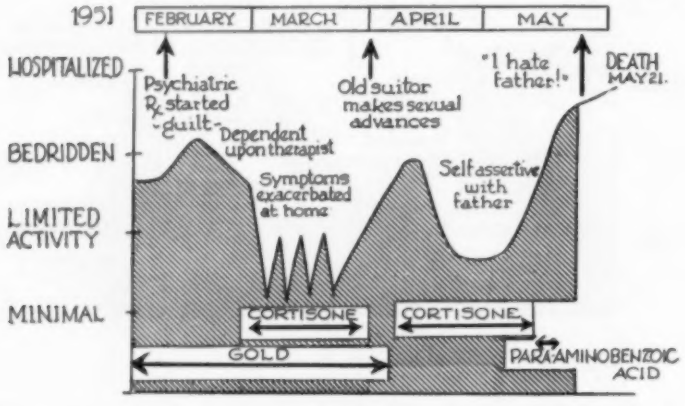

FIG. 3.

and threatened suicide. It was recognized at this time that she had a tremendous number of emotional problems, seeming to need a dependent relationship with her physicians which sometimes was openly erotic. This was accepted, as it seemed necessary for the prolongation of her life.

As it became more and more obvious that there was a direct relationship between the flare-up of her symptoms and emotional turmoil, psychiatric consultation was cautiously broached. Despite early resistance, the patient finally accepted the suggestion of this added approach in treatment. It was obvious, however, that she had no insight at the time into the relationship between symptoms and emotional factors.

As joint symptoms became more and more prominent, tapering of the fingers, with loss of subcutaneous fatty tissue, became fairly well advanced. At this time there was no doubt about the diagnosis of scleroderma. Because of a lack of response to a conservative program of treatment a course of chrysotherapy had been started on November 20, 1951, but it was not helpful.

Psychotherapy was formally begun on February 9, 1951. Her father objected strenuously to this additional approach in treatment, considering it an insult to her

intelligence as well as to the family's dignity. After consultation with the patient's internist and surgeon, however, he reluctantly acquiesced. During the first interview the patient was very sweet and ingratiating and obviously quite dependent, insisting that her nurse-companion accompany her into the psychiatrist's office, and throughout the hour constantly turning to this companion while relating the events of her life, seeking reassurance and support even in answering the simplest questions. This was done in a pleasing, childlike manner. She was very vague and evasive in giving her medical history, later saying that she "didn't want to hurt the psychiatrist's feelings." She referred particularly to her father's dislike of psychiatrists. There was an attempt to keep everything on a rather bland, matter-of-fact level, with the patient admitting neither fears nor resentment. Later she occasionally expressed a mild degree of anger toward people in her surroundings, particularly her father. This was immediately followed by remorse: "I should not be talking that way." By the third session she had obviously become quite attached to the therapist, as she had previously become attached to the internist and surgeon, and was able to talk in a cautious way about her father's violent objections to therapy.

Despite physical therapeutic measures she had begun in the interim to develop flexion contractures of several joints. Consequently, it was decided to give her a trial on cortisone. This drug was started on March 1, 1951, and continued through March 30, 1951. Subjectively she became about 85 per cent improved, and objectively showed some increase in motion of the elbows and shoulders. Hypertension was first noted at this time, however. She remained relatively free of pain throughout this period.

The patient was quite encouraged and became overtly euphoric over her improvement. During her psychiatric interviews she went into minute detail in describing the events of the day. It was noted by the therapist as well as by the patient that, despite the symptomatic improvement, whenever she felt chastised or criticized by her father the symptoms returned. On the other hand, she felt particularly well when out with friends and away from parental discipline. In a very childlike way she talked of sitting in a cocktail lounge with friends one evening and having two drinks, as if this were a risqué adventure. She began to express some self-assertiveness toward her father, and talked in a very hesitant way about emancipating herself from her family. Apparently this attitude was recognized by her children, who reinforced it by demanding that she have nothing to do with their grandparents as they (the children) did not want to visit them.

A few days after cortisone was discontinued her symptoms began to return and she suffered a very bad week, with an exacerbation of much of her muscle aching and joint stiffness. At this time she was again visited by the neighborhood doctor whom at one time she had planned to marry. He was again quite seductive in his behavior, bursting into her bedroom when she was dressed in only a thin nightgown, and sitting on the bed while being suggestively amorous. She rejected his advances and he, in anger, began ranting against her medical regimen, suggesting that she take narcotics freely to relieve her pain. He stated that everyone in her home town was ridiculing her for going to a psychiatrist. All of this led to a marked exacerbation of the symptoms and, when seen by the therapist, she was acutely disturbed and depressed, crying and stating that she did not want to go home. She required an extra therapeutic session before she could be calmed. Upon the patient's return home she found that her father had been talking to this doctor and had come to the conclusion that she should seek medical help elsewhere. He had become obstinate in his disapproval of psychiatrists. This was tantamount to pulling the rug from under her.

About the same time she developed a gold dermatitis, and consequently it was felt advisable to stop the gold. During the next few days the gold dermatitis became so much worse that she was advised to resume cortisone on April 16. This was

continued until May 3, and had a beneficial effect on both the rash and the signs of renal irritation which had developed.

While on the hormone the patient had made a relatively good adjustment, putting off her father's demand for a shift in physicians and discontinuance of psychiatric treatment, while becoming preoccupied with the emotional problems of her daughter, who rather suddenly had given up a passive, withdrawn adjustment at school and had become instead a behavior problem. The patient described several tender scenes with her daughter, remarking that the child was such a close companion, and that they could discuss their innermost secrets with each other. She contrasted this with her own relationship to her parents. At the same time she was showing more and more independent, self-assertive behavior, and was gently encouraged in this gradual emancipation by the therapist. A new symptom developed at this time, consisting of severe pain behind the right eye and headaches in the right temporal region. Joint symptoms had returned in almost full force, the blood pressure was 180/84 mm. of Hg, and grade II hypertensive retinopathy was noticed.

On May 11, 1951, when she next returned to the internist's office, there was a scene of tense emotional upheaval, precipitated by her father's absolute insistence not only that she give up her psychiatrist but also that she see other medical consultants. Her father had shown no understanding of the emotional problems involved. Despite frequent requests from the internist and psychiatrist, he would not consult with the psychiatrist directly, apparently considering psychiatric treatment as a blow to his own ego. The patient herself on this date was quite depressed, crying and complaining that she had had considerable difficulty getting on the train to come to the doctor's office. A large dose of Demerol was necessary to relieve her pain. While in this state the patient reported to the internist as follows: "Doctor, I hate my father, I hate everything he stands for. He has always tried to run my life and never allowed me to make any decisions of my own. The only few happy years I had were with my husband away from home. I hate to go to my father's home. He is continuously forcing me to do things I don't want to do. Every time I go near his home I feel much worse physically. I know it has a lot to do with the way I feel today." Following this there was an intense guilt reaction in which she openly expressed her remorse. Attempts were made to dilute the feeling of guilt. That evening her father called from home and seemed very kindly and solicitous. This aggravated her guilt reaction so that she could not sleep during the night and had an acute exacerbation of all symptoms. When seen the next day the patient was obviously acutely disturbed and would not talk directly about the anger she had expressed toward her father the preceding day, merely hinting at it in a very vague, indirect way. At that time it was felt absolutely necessary to get the father's cooperation, as the conflict between her dependency upon her father and the therapist was so intense that it was predicted this girl's symptoms might be exacerbated to the extent of leading to her early death.

Upon the patient's return home her symptoms became much worse. Her father ordered her confined to her bed under the constant care of her nurse, taking much of the medical management into his own hands and undermining her confidence in her physicians. At times she expressed somewhat bizarre grandiose ideas, stating: "I am being experimented on at the medical school because I am such an interesting case. They are seeing me for $20.00 an hour rather than $50.00 an hour." It was felt that this was just an accentuation of her previous personality, where she always adopted a somewhat unreal feeling of superiority. In spite of renewal of cortisone she rapidly became much worse and required narcotics for relief constantly. Her headaches, and especially the pain behind the right eye, became intense, and it was necessary to hospitalize her on an emergency basis on May 18. Examination at that

time revealed her to be acutely ill. Despite all medication there was a rapid downward course, terminated by a left hemiplegia on May 20, 1951.

During the terminal illness of the patient she was too sick to contact in a psychotherapeutic way. The father refused to see the psychiatrist at any time and on one occasion purposely walked out of the room when the psychiatrist entered to examine the patient neurologically. A good indication of the father's personality is a letter written several weeks after the patient's death. In a threatening tone he accused the psychiatrist of seeing the patient for only personal monetary gain, to the "worry, discomfort and ridicule of my daughter." In this letter the father demanded the return of all previous fees he had paid the therapist and a public apology.

Summary and Psychodynamics

This 35 year old woman was a warm, affectionate, demonstrative and overtly dependent individual whose behavior, despite its childishness, was pleasant and endearing. However, she exploited her personality and her serious incapacitating illness to demand constant love and attention from those in her environment. When loving tenderness was provided by her physicians, nurse-companion and children, her symptoms noticeably improved, whether she was on cortisone or not. However, when forced into contact with her austere, cold, controlling and dominating parents, especially the father, she became acutely ill, usually bedridden. Although this was obvious even to her children she refused to recognize the connection between her symptoms and her emotions until the terminal stages of her illness. Generally her attitude towards her parents was one of sweet ingratiation and constant protestations of her love and affection, particularly for her father. As treatment progressed it became obvious that her anger and resentment toward her father required constant suppression and was close to consciousness most of the time. At one point during the latter stages of her psychiatric care she actually openly expressed this rage, but quickly followed this up by expressing much remorse and repentance. Her needs for pleasure, demonstrated love and sexual gratification were obvious but constantly suppressed and hidden from her parents, who became threatening whenever these needs were manifest. At these times there would be an exacerbation of symptoms, a denial of these needs, and extreme guilt feelings for imagined past transgression. Except for the period of euphoria under cortisone, self-assertive behavior on the part of the patient was impossible.

The life history of this patient indicates that her first somatic symptoms (urticaria) occurred when she was about to marry and emancipate herself from the authoritative parental home. Her second serious illness occurred shortly after her husband's death and her return to the parental home (depression, chronic upper respiratory infection, tuberculosis). Her third, and ultimately fatal, illness (Raynaud's phenomena and scleroderma) occurred shortly after she had to renounce the sexual advances and marriage proposal of a married physician of whom her father did not approve.

Although there are numerous psychodynamic implications in the patient's relationship to her family, particularly her father, relatively sparse unconscious material does not warrant definite dynamic conclusions. It suffices to say that this woman never reached any high level of maturity or central integration, psychologically approaching very closely to a psychotic individual. Her conflicts were close to consciousness, requiring constant suppression, not being

repressed or alleviated by structural neurotic symptoms, but rather expressing themselves overtly in somatic disorders. The secondary gains of her illness were obvious in that it offered an opportunity to escape from the family to a more loving and affectionate atmosphere while at the same time maintaining a dependent rôle. It is particularly interesting to note that the illness this woman manifested was chronic and disfiguring and consequently a great blow to her self-esteem, which previously had been maintained to a large extent by her attractive, "doll-like" appearance.

In February, 1951, it became obvious to the internist and the surgeon treating this woman that drastic therapeutic measures were indicated if this patient was to survive. Consequently cortisone therapy was decided upon as well as psychiatric consultation. Both led to an immediate and dramatic improvement in the patient's condition. She had another person to depend upon, and immediately developed an erotic attachment to the psychotherapist. At the same time the cortisone gave considerable relief of her symptoms. Both resulted in a sense of well-being which verged on the pathologic. She manifested for the first time some self-assertive, independent behavior, which was reinforced by her children's enthusiasm for getting away from the grandparents. In the light of subsequent events it is obvious that this was a false independence, as the father, resentful of this new behavior in his daughter, insisted that she give up her present medical and psychiatric régime. The tenuous suppression of her rage and resentment towards her father as well as of her own guilty fears broke down in this situation, and for the first time the patient realized her tremendous hate for her family and all they stood for. This was immediately followed by an acute exacerbation of her symptoms, with a rapid progression to death. This case dramatically presents not only the physiologic dangers of cortisone therapy but also the psychologic factors recently emphasized by Rome and Braceland.[9] It is felt that the false sense of strength and independence developing under the drug precipitated this woman's deeper conflicts before she was capable of handling them psychologically. It also illustrates the importance of getting the family's complete coöperation in accepting psychiatric therapy, particularly in those cases that are emotionally tied to the family. If one does not do this the conflicts over treatment will only aggravate the already present anxieties.

No generalized conclusions can be drawn from one single case. There are, however, a number of interesting points to be made, because this patient shows many similarities to other so-called psychosomatic illnesses. There is more and more evidence that patients with psychosomatic illnesses show, as this patient did, a conscious or at least preconscious awareness of their deepest conflicts which requires constant suppression. Seemingly this represents an inability for the more economic repression and structuralization into definite neurotic symptoms. One could also speculate that somatic involvement of the skin and joints, with its crippling disfigurement, might have had particular meaning for this narcissistic patient, who had always been preoccupied with her personal appearance.

It is certain that she interpreted this disfigurement as a real disaster, an overwhelming threat to her security and self esteem.

Conclusion

1. A case of scleroderma is presented in which there are obvious emotional factors, both at the onset of the illness and coincidental with each flare-up of symptoms.

2. Cortisone in the doses used was helpful temporarily, relieving joint discomfort, increasing the mobility of the joints, and clearing up the dermatitis believed due to gold administration, but it seemed in no way to affect the basic course of the disease processes.

3. The psychologic dangers of cortisone therapy were emphasized, as this, along with conflicts over psychiatric treatment, seemed to precipitate deeper conflicts before the patient was psychologically capable of handling them.

4. The possibility that scleroderma is a disease of adaptation, a psychosomatic disorder, is raised. This case suggests that a precipitous awareness of unconscious conflicts can exacerbate the disease processes to such extent as to lead to a rapid generalization of the pathologic process and early death. Further study along these lines is indicated.

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RECURRENT BILATERAL SPONTANEOUS PNEUMOTHORAX TREATED WITH ARTIFICIAL HEMOTHORAX*

By Laurence A. Grossman, M.D., F.A.C.P., *Nashville, Tennessee*

Spontaneous pneumothorax of nontuberculous origin is frequently encountered. Often there is a single attack, from which the patient recovers uneventfully. Sometimes there are recurring attacks on the same or on the opposite side of the chest. Under such circumstances, treatment is indicated to prevent further recurrence if possible. Chemical irritation of the pleura to the end of obliterating the pleural cavity has been advocated. In 1906 Spengler [1]

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suggested the use of silver nitrate to induce adhesive pleuritis. In 1948 Brock [2] reported the successful treatment of several patients with recurrent pneumothorax by this method. Hypertonic glucose solution, gomenol-in-oil, talc and other irritating substances have also been used. More recently, Crenshaw [3] and Meade and Blades [4] have employed exploratory thoracotomy and surgical resection of blebs and bullae when the latter are demonstrable.

The instillation of blood into the pleural cavity to induce pleural symphysis was suggested in 1928 as a method of treatment by Watson and Robertson.[5]

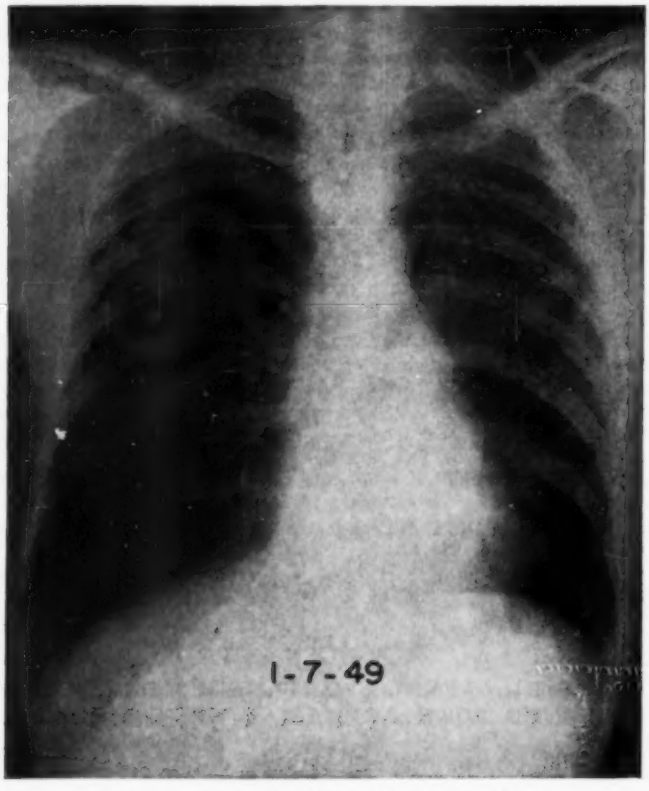

FIG. 1. Right pneumothorax (January 7, 1949).

Several subsequent communications on the subject were discouraging, and the method has been virtually abandoned. Nevertheless, this procedure seemed entirely satisfactory in the case at hand.

CASE REPORT

A 22 year old white man entered Vanderbilt Hospital January 7, 1949, complaining of severe pain in the right chest, shortness of breath and cough. Physical

signs and x-ray examination disclosed a pneumothorax with a marked degree of pulmonary collapse (figure 1). Twenty-four hours later, because of his increasing dyspnea, 1,500 c.c. of air were removed from the right pleural cavity. The patient was kept in bed. On January 21, upon awakening, he experienced severe pain in the left chest, radiating to the neck and to the left shoulder. X-ray revealed a partial collapse of the left lung (figure 2). The right pneumothorax had completely disappeared. The left lung rapidly reëxpanded. However, in rapid succession, the following episodes of spontaneous pneumothorax were observed (figure 3): February 7, and again March 30, left pneumothorax; May 20, right pneumothorax; June 13, left pneumothorax. In no instance did the degree of collapse exceed 25 per cent, and interval fluoroscopic and x-ray examinations always showed rapid reëxpansion. On July 8, he experienced extremely severe pain in the left chest. Pneumothorax could not be demonstrated. Eight days later he again developed right pneumothorax, with moderate collapse of the lung. It was decided then to attempt pleural symphysis on

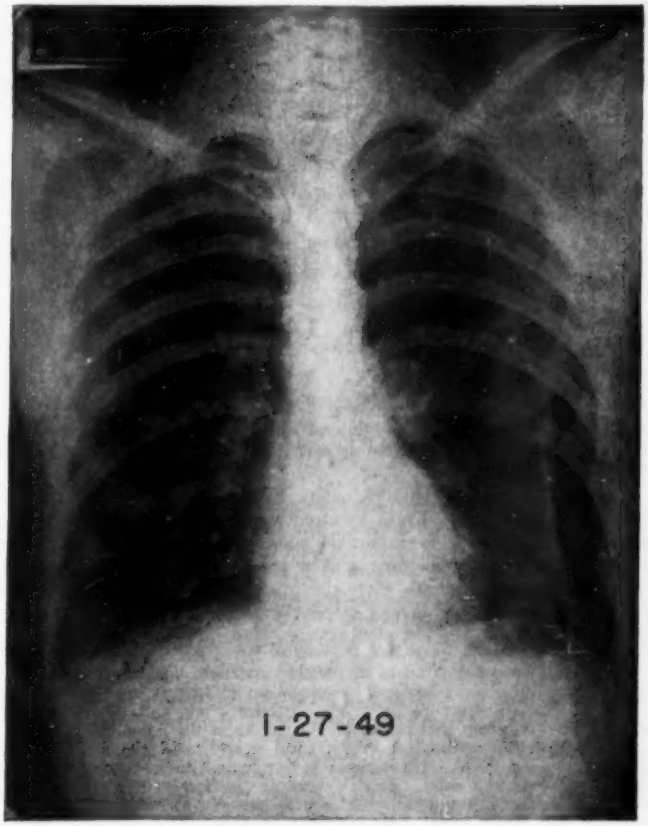

FIG. 2. Left pneumothorax (January 27, 1949).

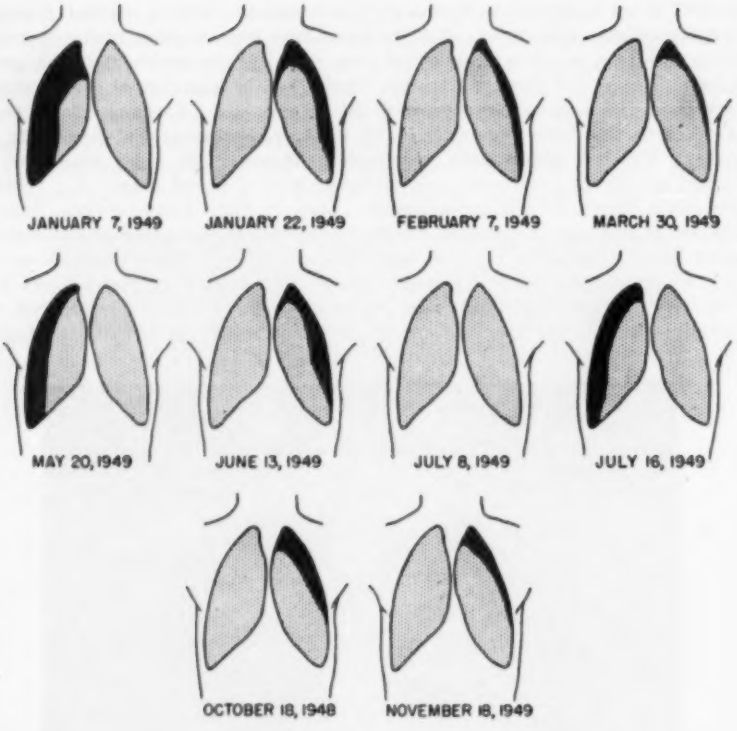

FIG. 3. Recurrent bilateral spontaneous pneumothorax.
Note: July 16, 1949, 25 c.c. blood injected into right pleural cavity. November 18, 1949, 25 c.c. blood injected into left pleural cavity. Period of observation: January 1, 1949, to April 3, 1953.

the right by injecting blood.* Eight hundred cubic centimeters of air were removed, following which 25 c.c. of the patient's blood were injected. Two days after the procedure the patient was ambulatory, and he promptly returned to work.

On October 18, three months after the injection of blood into the right pleural cavity, a small pneumothorax developed on the left side. An attempt was made to inject 50 c.c. of blood into the left pleural space, but this was unsuccessful because of

* An area in the second interspace at the midclavicular line was sterilized with iodine and alcohol. The skin and subcutaneous tissue were infiltrated with 1 per cent procaine solution. With a No. 20 gauge needle, a 3-way stopcock and a 50 c.c. syringe, the pleural cavity was entered. A clamp was placed on the needle at the point of emergence from the skin to prevent further insertion into the pleural cavity. As much air as possible was aspirated. Movement of the visceral pleura was felt against the needle point, and no further effort was made to withdraw air. Twenty-five cubic centimeters of blood were drawn from the antecubital vein and injected into the pleural cavity. The needle was then removed. The patient was then placed in the Trendelenburg position for 12 hours. Procaine penicillin was administered intramuscularly one hour before the procedure, and once daily for two days thereafter.

clotting in the syringe, and the procedure was abandoned temporarily. The patient improved rapidly. Nevertheless, on November 18, 1949, a left pneumothorax occurred spontaneously, resulting in approximately 30 per cent collapse of the left lung. Five hundred cubic centimeters of air were removed, and 25 c.c. of blood were introduced into the left pleural cavity. The patient became ambulatory the next day and since this treatment has remained well. He was last examined April 3, 1953.

Discussion

The ease and simplicity of therapeutic hemothorax, and such isolated experiences with it as are herein reported, make it worthy of additional consideration. There is no morbidity, and special equipment is not required. The use of blood for the production of pleural symphysis should probably be restricted to simple recurrent pneumothorax, and theoretically should be employed only when it is thought that the lung can fully reëxpand. Obviously, if pleural symphysis is to be produced, the lung must be expanded so that the visceral and parietal pleural surfaces are in contact when the blood is injected.

Although hemothorax is thought to produce pleural symphysis, there is no actual proof that adhesive changes between visceral and parietal pleurae ensue. The introduction of blood into the pleural cavity may simply seal off the tear in the visceral pleura. Subsequent artificial pneumothorax would demonstrate the presence or absence of pleural adhesions, and thus throw additional light upon the mechanism of recovery following this treatment. This procedure did not seem justified in the case at hand. In the presence of tension cysts, bullae or pleural effusion, this method of treatment probably should not be employed.

Summary

A case is reported of recurrent bilateral spontaneous pneumothorax successfully treated with instillations of blood into the pleural spaces. The ease, simplicity and effectiveness of this procedure would seem to justify its more extensive employment.

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GLUCOSE NEPHROSIS WITH RENAL FAILURE IN A PATIENT WITH LAENNEC'S CIRRHOSIS *

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A characteristic type of renal tubular epithelial damage has been described in both man and experimental animals following the intravenous administration of hypertonic sucrose solutions. This kidney lesion, generally known as "sucrose nephrosis," has been observed in association with other sugars in hypertonic solution including xylose, inulin and glucose. It has also been reported to have occurred in man following such substances in hypertonic solutions as acacia, creatinine, sodium sulfate and urea. Although repeated injections of hypertonic sucrose at frequent intervals can effect significant interference with renal function in man, it is generally considered that the renal lesion produced by hypertonic glucose solution is mild and reversible, and produces no significant interference with renal function.

The case to be reported is an instance of renal failure which developed in a patient with Laennec's cirrhosis who was administered unusually large amounts of hypertonic glucose over a 15 day period. The patient's clinical course was characterized by a nephrotic type of edema and by the development of laboratory evidence of severe renal impairment. At necropsy the patient proved to have Laennec's cirrhosis, and the kidneys, which were symmetrically enlarged, disclosed microscopic evidence of severe tubular hydropic change of the type characteristically seen in cases of "sucrose nephrosis."

CASE REPORT

A 60 year old white housewife was admitted to the Crouse-Irving Hospital on January 14, 1951, because of an enlarging abdomen and epigastric pain of one week's duration. Four years prior to admission she had complained of shortness of breath after rather strenuous exertion. Three years later she developed ankle edema and was placed on digitalis and ammonium chloride, and occasional intramuscular injections of a mercurial diuretic. Approximately one month prior to admission her skin became light yellow in color and she vomited 2 tablespoonsful of bright blood. Hospitalization was advised but she refused and voluntarily discontinued all medications. Her ankle edema and dyspnea progressed, and she developed increased anorexia and weakness. One week prior to hospitalization she first noted abdominal enlargement, which progressed rapidly and was accompanied by intermittent sharp epigastric pains.

The patient denied alcoholic intake except for social drinking, although relatives stated that she was accustomed to taking large quantities of alcoholic beverages, often going without food for many days at a time. She was said to have eaten very little during the month prior to admission to the hospital.

Her past history revealed scarlet fever and typhoid fever in her youth, both without known sequelae. There was no family history of cardiac, liver or renal disease.

On admission the patient showed evidence of recent loss of weight, and appeared chronically ill. The skin was icteric. The temperature was 98.6° F., the pulse 120 per minute, respirations 28 per minute, and blood pressure 134/74 mm. of Hg. There

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were scattered spider angiomata over the back and shoulders, and there was no axillary hair. The sclerae were icteric and the conjunctivae were slightly pale. There were distended veins over the anterior chest, but the neck veins were not prominent. Chest expansion was normal. The diaphragms were high bilaterally and there were a few moist râles at the right base. The left border of cardiac dullness was detected 12 cm. from the midsternal line in the fifth intercostal space. Sounds were normal in rhythm and force, and no murmurs were heard. The abdomen was markedly distended, with bulging of the flanks and prominent superficial veins. A fluid wave was present. No organs or masses could be felt. There was 3 plus pitting sacral edema and 4 plus pitting edema of the lower extremities. A rectal examination disclosed yellow-colored stool on the examining finger.

Initial laboratory data revealed a hematocrit of 32 per cent, hemoglobin of 10 gm. per cent, white count of 9,600 per cubic millimeter, and a normal differential count. Urine was acid, with specific gravity of 1.010. There was no albumin or sugar present, and microscopic examination of the sediment was negative. Bile was present in the urine but urobilinogen was absent at 1:20 dilution. Fasting blood sugar was 93 mg. per cent; nonprotein nitrogen, 33 mg. per cent. The serum bilirubin was 3.1 mg. per cent "direct" and 5.7 mg. per cent "indirect." Cephalin flocculation was 4 plus, prothrombin concentration was 76 per cent, and the alkaline phosphatase was 7.4 Bodansky units. Total proteins were 6.7 gm. per cent, with 3.8 gm. per cent albumin and 2.9 gm. per cent globulin. Stool guaiac test for occult blood was positive. Electrocardiogram revealed a sinus tachycardia with occasional supraventricular complexes, plus marked clockwise rotation of a horizontal heart. A roentgenogram of the chest revealed elevated diaphragms with displacement to the left and upward of what appeared to be a normal heart. The lung fields were clear.

The patient was considered to have portal cirrhosis and was placed on a low salt, high calorie, high carbohydrate and high protein diet, with parenteral supplements of vitamins B, C and K. An abdominal paracentesis on January 15 produced 9,200 c.c. of clear amber fluid with specific gravity of 1.005. Pathologic examination of the fluid revealed occasional red blood cells, lymphocytes and mesothelial cells. No viscera were palpable after paracentesis. The patient lost 34 pounds in the first week with the aid of two injections of Mercuhydrin (2 c.c. on January 16 and 18). Despite encouragement and supervision the patient failed to take more than 1,000 calories daily. On January 20 an attempt was made to pass a Levine tube into the stomach for feeding, but had to be discontinued because of hematemesis thought to be due to irritation of esophageal varices. The patient was returned to oral feedings with low sodium protein supplementation, and supplemental intravenous infusions were administered. The frequency and amounts of fluids so administered are shown in chart 1. The patient became confused and weaker, and her course was characterized by decreasing food intake and repeated emeses of small amounts of bright blood. She also began to pass dark clotted blood by rectum. She remained afebrile, but penicillin was added to the regimen in view of the persistence of râles in the right lung base. On January 31 she became more confused and generally edematous, despite careful regulation of fluid intake and output. At this time the hemoglobin was 8.5 gm. per cent and the white count 16,500 per cubic millimeter, with 91 per cent polymorphonuclear leukocytes and 9 per cent lymphocytes. Urinalysis after glucose infusion revealed 1 plus albumin and 1 plus sugar. The microscopic examination showed many white cells. A nonprotein nitrogen was 322 mg. per cent, and CO_2 combining power was 33.2 vol. per cent. The serum bilirubin was 1.8 mg. per cent "direct" and 1.8 mg. per cent "indirect," and the cephalin flocculation was 4 plus. The serum protein was 6.3 gm. per cent, with 3.9 gm. per cent albumin and 2.4 gm. per cent globulin. The urine output decreased gradually, and the patient became comatose and died on February 3 after a massive hematemesis.

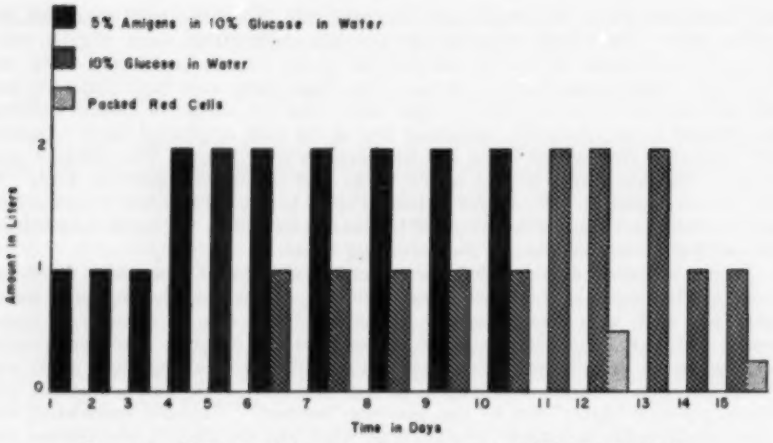
5% Amigens in 10% Glucose in Water
10% Glucose in Water
Packed Red Cells
Amount in Liters
0
1
2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time in Days

CHART 1. Nature and amount of intravenously administered fluids.

Gross Necropsy: The most significant external observation was the anasarca. Proptosis was apparent, and the tongue was the site of marked edema. The abdomen was markedly swollen, with approximately 3,000 c.c. of serous, straw-colored fluid in the peritoneal cavity. The heart weighed 300 gm. and was flabby in consistency.

FIG. 1. Gross appearance of the liver, showing the nodularity consistent with advanced Laennec's cirrhosis.

The valves and coronary arteries were not remarkable. The lungs were slightly heavier than usual and their cut surfaces disclosed moderate pulmonary edema. The spleen weighed 300 gm. and had a thickened capsule and its cut surface was soft and very moist. The liver weighed 1,500 gm. and was tan in color, and the external and cut surfaces were characterized by multiple nodules of rather uniform size, averaging about 1 cm. in diameter (figure 1). Small varices were noted within the esophageal mucosa, and the entire large bowel was the site of superficial ulcerations and many pinpoint hemorrhagic foci. Each kidney weighed 300 gm. and the capsules could be stripped readily, disclosing a smooth, olive-colored surface. On section the cut surface bulged, the cortex measured over 1 cm. in thickness, and the interlobular arteries were prominent (figure 2). The uterus was the site of a large subserous fibroid

FIG. 2. Cut surface of the kidney, demonstrating the marked increase in width of the cortex.

on its posterior surface. All other organs, including the brain, revealed nothing unusual grossly. The gross anatomic diagnoses were Laennec's cirrhosis, anasarca, uremic enteritis, and nephrosis of undetermined type.

Microscopic Examination: The liver was characterized by marked nodularity with distortion of the architecture. The nodules of liver cells were separated from one another by broad bands of highly vascularized connective tissue in which many chronic inflammatory cells were present. Some apparent bile duct proliferation was noted, and there was evidence of bile stasis within the biliary canaliculi. The hepatic cells showed moderate fatty change, and rare hyaline so-called "Mallory's bodies" were noted within the cytoplasm of some cells.

The kidneys were characterized by a severe hydropic degeneration, confined chiefly to the epithelium of the proximal convoluted tubules, although the change was occasionally noted within the thin limb of Henle and the distal convoluted tubular epithelium (figures 3 and 4). The affected cells were enormously swollen and bulged into the lumens, causing them to appear nearly obliterated. The cell membranes were

indistinct and the cytoplasm was replaced by a diffuse fine vacuolation of uniform size. Nuclear abnormalities were not striking, although some nuclei appeared pyknotic and shrunken. The affected tubular epithelium did not stain positively for either glycogen or fat. Fine granular material and leucine-like crystals were noted within the lumen of some convoluted tubules. Bowman's spaces were somewhat dilated and contained granular, pink-staining material. Other microscopic findings were esophageal varices and a leiomyoma of the uterus.

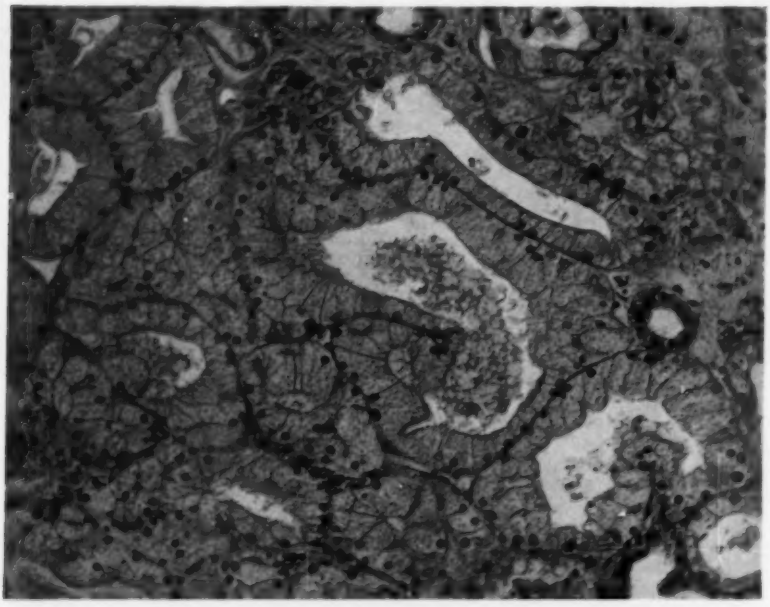

FIG. 3. Low power magnification of the kidney, showing the tubular distortion and swelling. Hematoxylin and eosin stain, × 122.

DISCUSSION

Early in 1930 the use of certain hypertonic solutions for the relief of tissue dehydration and the production of diuresis became widespread. Ten to 50 per cent sucrose administered intravenously was found to be the most effective of these hypertonic solutions as therapy for such conditions as cerebral edema resulting from trauma, acute alcoholism, chronic hypertensive states and acute glaucoma. Other preparations used were hypertonic sodium chloride and hypertonic glucose.

In 1933 Helmholz [1] investigated the effects of intravenously administered hypertonic solutions on the kidneys of experimental animals. His study was prompted by a necropsy examination of an eight year old boy who had been given repeated injections of 20 per cent sucrose for the relief of increased intracranial pressure. Severe hydropic degeneration of the convoluted tubules and ascending

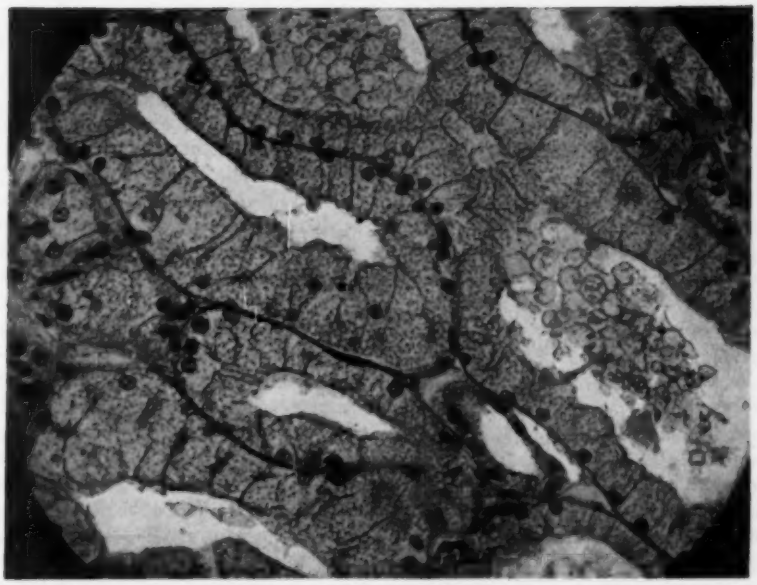

FIG. 4. Higher power magnification of the kidney, showing the finely distributed hydropic vacuoles within proximal convoluted tubules. Hematoxylin and eosin stain, × 173.

limb of the loop of Henle, with marked narrowing of many of their lumens, was found. Using rabbits, Helmholz found that the repeated injection of hypertonic solutions of sucrose at frequent intervals produced marked anatomic changes in the kidneys, with subsequent impairment of renal function as measured by the excretion of phenolsulfonphthalein. Other investigators corroborated this work. Lindberg [2] reported similar changes in the kidneys of dogs when he compared necropsy sections with the normal biopsy specimen taken before the injection of hypertonic sucrose. He found that the morphologic changes were transitory unless prolonged repeated injections were used. In addition, there was marked inconsistency between the amount of change seen and the degree of impairment of renal function.

Renal lesions occurring in man after the injection of sucrose were subsequently described by Cutler,[3] Anderson and Bethea [4] and Anderson.[5] Cutler's study implied that glucose might also produce the renal tubular lesions, but no account of the doses and frequency of administration was given, and no attempt was made to correlate the degree of tubular hydropic degeneration at necropsy with the amount of hypertonic solutions used. He stated that hydropic changes were found in the kidneys of 11 of 320 necropsy cases, and that 54.5 per cent of the 11 patients had received hypertonic solution of glucose in the week preceding death. Recently Berthoud [6] administered hypertonic glucose solution intravenously to 68 "terminal" subjects without obvious renal disease and found no striking histologic alterations in the kidneys of these patients. Cloudy swelling was frequently observed, but the severity of the process was not indicated. Fur-

thermore, no mention was made of the dose per kilogram of body weight, rate of administration, or the presence of other conditions which might possibly influence the degree of metabolism of glucose.

With regard to the pathogenetic mechanisms of these changes, Wilmer [7] showed that in the aglomerular toadfish, which cannot secrete sucrose, the sugar given intraperitoneally did not produce a nephrotoxic effect. He deduced from this that the hypertonic sucrose did not injure the tubule from the vascular side. When reabsorption of sucrose was blocked in phlorhizinized rabbits and rats, characteristic tubular changes occurred, suggesting that toxic injury was not dependent on tubular reabsorption of the sucrose. He theorized that the small amount of sucrose which diffused into the tubular cells (even in phlorhizinized animals) was the mechanism of damage. It has since been found that many compounds, if present in sufficient molar concentration in the renal tubules, may produce the changes described. Allen [8] suggests that the term "osmotic nephrosis" be used, since he believes that the changes within the tubular cells are the direct result of the disturbance of the normal osmotic relationships across the renal tubular cell membrane. Based on the premise that lesions are due to an abnormally high concentration and effective osmotic pressure of a substance presented to the tubular cells in the glomerular filtrate, he was able to explain why lesions are easy to produce with hypertonic sucrose and difficult to produce with hypertonic glucose. Glucose is metabolized, in contrast to sucrose, and, in addition, is reabsorbed by the renal tubules to a greater degree. However, in a clinical situation where glucose is not well metabolized, and large quantities of it are given in hypertonic solution, higher concentrations reach the tubules. It is this mechanism which is postulated as the cause of "osmotic nephrosis" in certain "susceptible" diabetics. Our patient had a markedly diseased liver, and while attempting to improve this patient's nutrition we failed to consider whether the liver could effectively metabolize the quantities of glucose presented to it.

In man and animals alike there appears to be a wide variation in susceptibility to the intravenous injection of sucrose. In humans as little as 50 gm. in one day have produced the typical renal lesions in some, whereas 250 gm. have failed in others. The variability of susceptibility has led to speculation that other factors may be important. The state of hydration was investigated by Rigdon and Cardwell,[9] who found that the quantity of sucrose necessary to produce the renal lesions in rabbits was much less when the animals were in a dehydrated state. However, this has not been confirmed either in dogs or in man.

Previous renal damage might be speculated upon as a necessary prerequisite for this type of kidney lesion. However, the typical lesions of "sucrose nephrosis" have been experimentally produced in previously normal kidneys of rabbits and dogs. Hypertonic sucrose was administered to 21 patients with hypertension of long duration by Murphy et al.,[10] with no subsequent clinically measurable renal damage. It is pertinent to emphasize that the kidneys of the patient reported herein showed no evidence of previous renal disease.

Finally, no relationship between the severity of hydropic changes in the kidneys and the age of the patient, blood pressure, type of operation, anesthetic agent or disease has been found. It is agreed, however, that one factor—the total

dose of hypertonic solution administered—is of utmost importance. The patient we are reporting received a total of 3,000 gm. of glucose in 15 days, averaging 200 gm. daily, more than double that administered by Berthoud. Cutler estimated that 6 to 10 gm. per kilogram of body weight per week was the usual dose of sucrose sufficient to produce the tubular changes. After paracentesis our patient weighed 152 pounds, and she received an average of 21 gm. of glucose per kilogram of this weight per week for two weeks. It is possible that, in the presence of the markedly abnormal liver, metabolism of glucose was sufficiently impaired that high concentrations appeared in the renal tubules, causing the renal lesions described above.

Summary

An instance of renal failure with the production of the nephrotic type of edema in a patient with Laennec's cirrhosis is reported. Large amounts of intravenous hypertonic glucose solution were administered in an effort to improve the nutritional status of the patient. At necropsy microscopic evidence of severe renal tubular damage of the type seen in "sucrose nephrosis" was observed. Although renal tubular changes similar to the case herein described, but of lesser severity, are not infrequently seen at necropsy in patients to whom intravenous glucose had been administered prior to death, the present case is believed to be the first instance recorded in the literature of glucose nephrosis with resultant renal failure.

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THE CYTOLOGIC DIAGNOSIS OF DUODENAL SARCOMA (POLYMORPHIC RETICULOSARCOMA) *

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INTRODUCTION

THE rarity of duodenal sarcoma has been repeatedly stressed by various authors,[2, 3, 5, 9, 13, 14, 21, 26] and the literature consists primarily of single case reports.[2, 6, 11, 12, 24, 27, 32] We add another case report to show how a definitive preoperative diagnosis can be made by the cytologic method. In the past the clinical diagnosis of this condition was infrequent because obstructive symptoms in small bowel sarcoma are unusual in contrast to carcinoma. The roentgenologic diagnosis of these tumors has been carefully evaluated by Freud,[10] who found correct diagnosis most difficult. The lack of stenosis, in Grilli's [12] opinion, is the main reason for failure of radiologic diagnosis. Ullman and Abeshouse [33] found only nine correct preoperative diagnoses in a series of 126 cases (two clinical, seven x-ray).

INCIDENCE

The first case of sarcoma of the duodenum apparently was reported by Alexander (cited in [27]) in 1877. Libman [20] found 15 duodenal sarcomas in 42 lymphomas of the small intestine. Ullman and Abeshouse [33] had only four in their 126 cases. Prey, Foster and Dennis [27] in 1933 gathered 61 cases from the whole literature. According to Leichener (cited in [32]), the ratio between carcinoma and sarcoma of the duodenum is 10:1. Astfel (cited in [2]) found the incidence of duodenal malignancy to be 0.033 per cent in 130,721 autopsies. The same incidence is given by Eger (cited in [2]) in autopsy material gathered from different European hospitals. In 20 years there were only two cases of lymphosarcoma of the small intestine published in Belgium, though more frequent single case reports are found in the French literature.[18, 21] No malignant lymphomas of the duodenum were found in Faulkner's [9] series from the Mayo Clinic.

CASE REPORT

This 39 year old man was seen by one of us (F. J. O.) in the Billings outpatient gastrointestinal clinic because of intermittent vomiting of four years' duration. Four years before he had had an episode of vomiting one night. He had similar episodes every two to three months thereafter. For the past six months these attacks had increased in frequency and severity. The patient's vomiting might occur two to three hours after meals, but at other times was unrelated to food. He had a sensation of fullness but no pain, hematemesis or melena. He had lost about 30 pounds.

There was a question of slight jaundice four months before, but no acholic stools. The patient was hospitalized elsewhere and at that time a gastroduodenal

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† Damon Runyon Fellow.

x-ray was said to reveal "a little ulcer in the duodenum and a narrow opening" of the stomach. The blood picture was normal, and free hydrochloric acid was present in the gastric secretion. He was put on milk and crackers, and other food was gradually added. He experienced some relief from vomiting for a month and gained weight. He then started to vomit again. A month prior to admission he was vomiting after every meal and could drink only liquids. His appetite remained good and there was no change in bowel habits. He lost another 25 pounds. Physical examination showed a pale, chronically ill young man with foul breath and cheilosis. Temperature, pulse, respirations and blood pressure were normal. Examination of the chest and abdomen was negative. The initial clinical impression was incomplete obstruction due to duodenal ulcer. Complete blood counts were normal. The stools were benzidine-positive three times on a meat-free diet. Blood sodium, potassium, CO_2 and pH were within normal range. The highest basal specimen of gastric juice showed 37 clinical units of free hydrochloric acid.

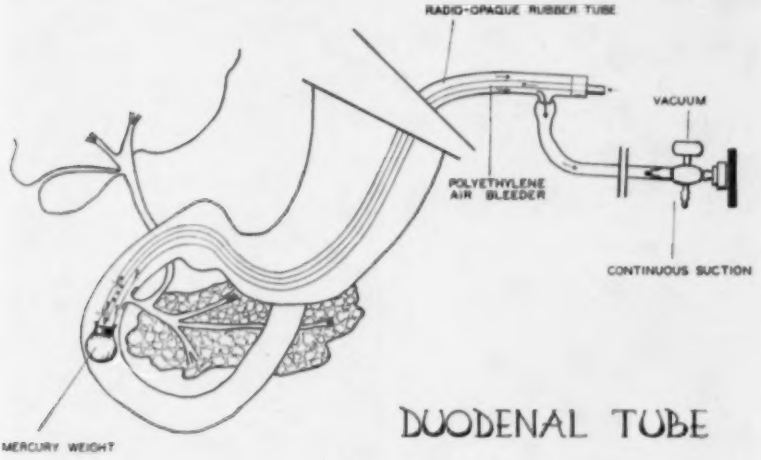


FIG. 1.

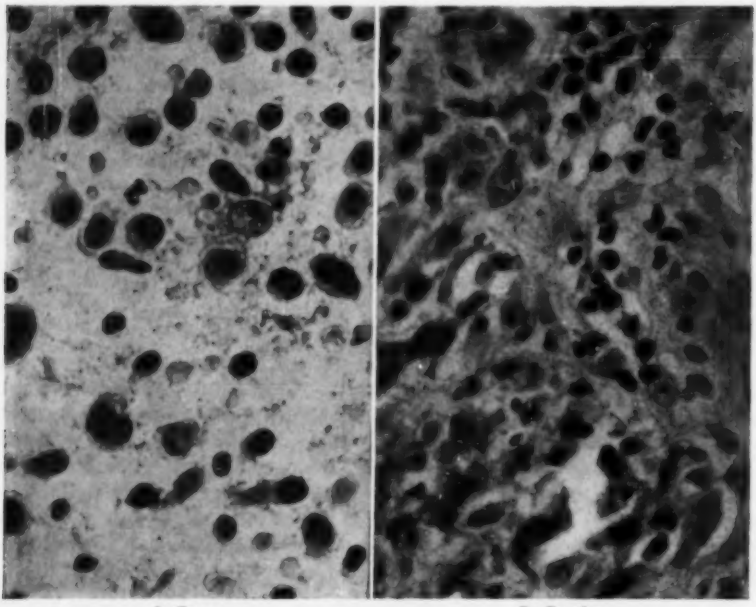
Our first gastroduodenal x-ray examination was interpreted as showing a normal esophagus, stomach, duodenal bulb and second portion of the duodenum. Some apparent narrowing of the ascending loop of the duodenum was seen to fill out to normal dimensions at fluoroscopy. The colon and the terminal ileum were normal. The responsible clinician (F. J. O.), on reviewing our films as well as the outside films, suspected a narrowed area in the fourth portion of the duodenum. The diagnoses now considered were lymphoma and regional enteritis.[4]

At this point cytologic examination was performed by one of us (C. E. R.). These studies made the decisive preoperative diagnosis. A description of our modifications of Lemon's [10] duodenal cytologic technic may be of interest.

The patient must be meticulously prepared. Even subclinical obstruction will contaminate the slides with food and make the examination unsatisfactory. Liquid diet and continuous aspiration for 24 hours are usually necessary in obstruction. An overnight fast is sufficient preparation for the unobstructed patient. For comfort the patient may gargle with a safe local anesthetic, such as 1 per cent Benadryl or Pyribenzamine, prior to passage of the tube. No oily material should be used to

lubricate the tube, since this may cause the cells to fall off the slides when fixed in ether-alcohol (a fat solvent).

A mercury-tipped tube is passed into the duodenum and its position checked by fluoroscopy. Gravity drainage may be employed, but this method necessitates constant attention by the operator to maintain patency of the lumen and to insure collection of the maximal volume. Incorporation of a bleeder inner-tube [7] (figure 1) prevents the tube from plugging and frees the operator for other work. Amyl nitrite, intravenous secretin and Decholin are successively administered to secure maximal drainage from the liver, biliary tract and pancreas in an effort to diagnose malignancy of these organs. Not more than five to 10 minutes are allowed to elapse between aspiration and fixation of the smear of the cellular sediment. During this



A. Smear *B.* Section

FIG. 2.

waiting period the aspirate is packed in ice to slow enzymatic digestion. Centrifugation is accomplished in three minutes at 5,000 r.p.m. in an angle head centrifuge using 50 c.c. plastic cups. A modification of the Papanicolaou stain [20] is used which insures cell adherence in spite of the detergent action of bile.

Diagnostic cells were found in this case by the routine duodenal drainage described above. A better cytologic picture was subsequently obtained by passing the tube into the involved fourth portion of the duodenum and lavaging the area vigorously with Ringer's solution. Rubin et al.[21] have described the cytologic criteria by which they diagnosed three sarcomas and one Hodgkin's disease of the stomach. All these criteria were fulfilled in this case (figure 2A). The most distinctive sarcomatous feature was the distribution of the malignant cells singly rather than in clumps, as is usual in carcinoma. The malignant cells showed some variation in size

FIG. 3. X-ray—duodenal loop.

but for the most part were uniform. There was a rather complete spectrum of the lymphatic series from normal mature cells to obvious primitive malignant forms. The malignant cells showed the usual features: increased ratio of nucleolar to nuclear area and of nuclear to cytoplasmic area, increased size and number of nucleoli, prominent nuclear membrane and increased nuclear chromatin. The cytoplasm of the malignant cells was very scant and often hardly discernible. There were many red blood cells and a fair number of polymorphonuclear leukocytes. The malignant cells were thought to be of reticuloendothelial origin, and the cytologic report was simply "lymphosarcoma." In the present state of our knowledge we do not attempt a more specific diagnosis as to type and histologic classification, since this complex field is far from being settled even in the minds of pathologists.[1, 14, 15, 28]

FIG. 4. Jejunum infiltrated by tumor.

A second upper gastrointestinal x-ray examination was performed after the cytologic study. This time the ascending portion of the duodenum was found to be narrowed to about half the normal caliber. The mucosa seemed destroyed in the fourth portion of the duodenum; there were large nodular masses in the dilated third portion of the duodenum. The roentgenologist felt that a carcinoma of the duodenum was the most likely diagnosis, but carcinoma of the pancreas and lymphoma were not excluded (figure 3).

Laparotomy three days later revealed a striking thickening and firmness of the second and third portion of the duodenum continuing into the first portion of the jejunum. Less severe thickening and edema were noted also in the next two feet of jejunum. The lymphatics of this part of the small intestine were prominent, and numerous 1 cm. diameter lymph nodes were felt at the base of the mesentery. The pancreas was normal. Some involved nodes and the proximal jejunal wall were biopsied. A palliative gastroenterostomy was performed.

The patient recovered uneventfully from operation. A series of x-ray treatments was administered postoperatively. He is not doing too well currently.

The gross biopsy specimen showed an ulcerated portion of intestinal wall. The microscopic description by one of us (M. B. G.) follows: There was extensive destruction of the mucosa. Only a few glandular elements remained (figure 4). The mucosa was almost completely replaced by very cellular tumor tissue. The cells, which seemed free and isolated, were enmeshed in delicate, scant reticulum. A high power of one of the sections (figure 2B) shows cells similar to those found in the smear (figure 2A). In some regions the large reticuloendothelial type of cell was prevalent and there was syncytium formation with multiple nuclei and undivided protoplasm. In other areas the cellular pattern was quite similar to Hodgkin's granuloma, with Sternberg-Reed cells and somewhat larger hyaline trabeculae. Diffuse, inflammatory infiltration with an accumulation of plasma cells and eosinophils was noted near the eroded surface of the specimen. Impression: polymorphic reticulosarcoma, also known as reticulosarcoma-mixed type or Hodgkin's sarcoma, following the classification of Robb-Smith.[28]

Discussion

Exfoliative cytology has been used to diagnose cancer of the stomach for over a half century. There has been a recent re-awakening of interest in this method; its value in cancer diagnosis throughout the digestive tract is summarized elsewhere.[25, 29] Recent work of Lemon[16, 17] and others[22, 23, 30] has shown the diagnostic value of cytologic examination of the duodenal contents. Although the accuracy does not approach that obtained in the stomach and colon, any aid is welcome in diagnosing the inaccessible malignancies of the liver, biliary tract, pancreas and duodenum. This method should also prove useful in differentiating benign from malignant lesions found throughout the small bowel by x-ray. The potentialities of this procedure justify more widespread use.

Summary

A preoperative cytologic diagnosis of polymorphic reticulosarcoma of the duodenum is described. The cytologic technic of duodenal drainage is set forth in detail. Cytologic criteria of sarcoma are outlined.

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A CASE OF THE SENEAR-USHER SYNDROME TREATED WITH ACTH AND CORTISONE *

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INTRODUCTION

In 1926 Senear and Usher [1] described "An Unusual Type of Pemphigus, Combining Features of Lupus Erythematosus." They presented four cases and reviewed seven others from the Transactions of several dermatologic societies. In essence, these were patients with lesions on the face that resembled lupus erythematosus and with lesions on the trunk that resembled pemphigus. Furthermore, it appeared that patients with this combined dermatitis had a prognosis considerably better than patients with either pemphigus or lupus. If nothing else, this fact singled out this syndrome as being of more than academic interest. Ormsby [2] suggested the name "pemphigus erythematodes." Since then some have considered it as an entity, sometimes diagnosable only after long observation,[3] and some have considered it as a variant of pemphigus.[4]

CLINICAL PICTURE

The clinical picture includes dermatologic features of both lupus erythematosus and pemphigus.

The manifestations resembling lupus erythematosus on the scalp and face consist of chronic discoid erythematous lesions with carpet-tack scaling, or lesions not unlike a congested seborrheic dermatitis. These facial manifestations are frequently found over the nose and malar eminences, the so-called "butterfly area" of the face. They are further notable for their evanescence and their tendency to rapid change from the more chronic to the more acute type.

The pemphigus-like lesions appear on the trunk and extremities. The primary lesion is a bulla, usually small, flaccid and thin-roofed, which tends to rupture easily, giving rise to two other types. The first of these is a reddish, raw patch denuded of epidermis. As a result of coalescence of these lesions, larger patches, sometimes reaching the size of a palm, may form. The second variety consists of lesions covered with thin, greasy, yellowish scaling crusts, suggesting either an extremely greasy seborrheic keratosis or an impetiginous or a psoriatic lesion. These involute, as a rule, leaving pigmented patches. Fresh bullae may develop in these pigmented areas.

TREATMENT

Many forms of therapy have been used, probably due to the basic inefficacy of all therapy. Temporary responses have been reported with acetarsone,[5] aureomycin, and a host of other materials. In a discussion of pemphigus, Rattner [6] lists five topical antiseptics, at least four arsenicals, penicillin, sulfonamides, naphuride sodium, liver substance, vitamin D, blood transfusions, x-ray

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therapy to the liver and spleen, sedatives, adrenal extract and smallpox vaccine as possible therapeutic measures.

In view of the reported favorable results with adrenal steroids in cases of pemphigus, it was decided to observe the response of this syndrome to ACTH therapy.

Case Report

The patient was a 79 year old woman who developed a pruritic scaly eruption on the face and nose in August, 1949. She was treated for seborrheic dermatitis, with slight improvement. One year later her nose became reddened, with development of telangiectasia on the tip. The diagnosis of a chronic discoid lupus erythematosus

Fig. 1. Face, after second course of corticosteroid therapy, illustrating the persistence of the lupus erythematosus-like lesions.

was entertained. Therapy consisted of bismuth injections and vitamin A and D ointment locally, without improvement. Pruritic bullae began to develop on the back, postauricular and periumbilical areas soon afterwards. She was then admitted to Maimonides Hospital for further investigation and therapy. The past history was negative except for hypertension without evidence of congestive failure.

Physical examination was notable mainly for the skin lesions. On the face they were erythematous, scaly and dry, and extended over the "butterfly area," most markedly on the nose. The mucous membranes of the mouth were not involved. On the chest, periumbilical area, back and postauricular areas and in isolated regions of the arms and legs were grouped lesions varying from 2 to 5 cm., which were encrusted and erythematous. Fresh bullae, some on a nonerythematous base, and some recently broken bullae were noted. The Nikolsky sign was negative.

Various laboratory tests showed only a mild anemia with 80 per cent hemoglobin. Biopsy of a lesion on the back showed vesiculation in the stratum corneum and areas of acanthosis. A preparation for "L. E." cells was negative.

After two weeks of hospitalization no improvement was noted. Therapy with ACTH, 20 mg. daily in an eight hour intravenous infusion of 1,000 c.c. of glucose solution, was then begun. There was gradual improvement, first in the face lesions, where less erythema and scaling were noted. Fresh bullae continued to form on the body, though there was less itching. After three weeks of therapy no new bullae

FIG. 2. Body, after the second course of corticosteroid therapy, illustrating the flat, pigmented residue of the pemphigoid lesions.

were seen on the trunk, and the old lesions showed pigmentation only, with no crusting. Therapy had to be discontinued after one month due to the development of mental aberrations and tonic convulsive movements, which ceased after ACTH was discontinued. Four weeks after cessation of ACTH therapy only a few new bullae had formed. The patient was discharged with a diagnosis of Senear-Usher syndrome, improved.

One month later, she was admitted to another institution because of exacerbation of the lesions. On physical examination, fresh bullae were noted on the trunk, and

the facial lesions were similar to those described on admission to Maimonides Hospital. She was again treated with ACTH, 25 mg. daily, but fresh bullae continued to form until the dosage was increased to 35 mg. daily. Therapy was then changed to cortisone, 100 mg. per day by mouth. After four and one-half months of this second course of corticoid therapy the trunk and extremity lesions were much improved: flat, red-brown, discrete areas with slight pruritus were noted on the back, chest, abdomen and limbs. The facial lesions, however, had progressed and presented erythematous, confluent areas on the nose and cheeks.

Discussion

The case above reported has many of the features of the so-called Senear-Usher syndrome. The patient's skin lesions probably began in 1949 and, despite their full development over the subsequent three years, there was no systemic illness accompanying them. The facial lesions strongly suggested lupus erythematosus, while the trunk and limbs showed typical pemphigus-like lesions. There were no oral manifestations.

Therapy with ACTH was instituted in view of absence of consistently good results with previously reported forms of therapy, and in view of promising reports in cases of pemphigus treated with ACTH or cortisone.

The two types of lesions responded somewhat differently to corticoid therapy. The facial lesions showed a moderate decrease in scaling and erythema after the first course of ACTH, but progressed steadily during the second course. The pemphigus-like lesions responded well to both courses, with a decrease of new bullae formation and of pruritus, and eventuated in flat pigmented, discrete, healed lesions. It is possibly noteworthy that a larger dose of ACTH was necessary to produce the partial remission the second time. The only toxic effects noted were neuropsychiatric aberrations during the first hospitalization, which ceased after discontinuance of ACTH. These did not recur during the second course of treatment.

Summary

A case of the Senear-Usher syndrome is described, treated with ACTH and cortisone. Two separate partial remissions were observed, more marked in the pemphigus-like lesions of the trunk than in the lupus erythematosus-like lesions of the face.

Acknowledgment

Grateful acknowledgment is made to the memory of Dr. Emanuel B. Schoenbach, late Director of the Medical Services of the Maimonides Hospital, for his suggestions and encouragement in the preparation of this report.

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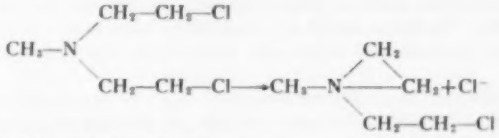
NITROGEN MUSTARD THERAPY COMPLICATED BY ACUTE RENAL FAILURE DUE TO URIC ACID CRYSTALLIZATION *

By Glenn H. Richmond, Captain, MC, and Grant D. Beardsley, 1st Lieutenant, MC, *Tacoma, Washington*

Since the first clinical use of nitrogen mustard compounds in 1942,[1] hundreds of articles have appeared in the medical literature to attest its value in the palliative therapy of Hodgkin's disease, lymphosarcoma, chronic leukemia and other neoplastic diseases. The narrow margin between the toxic and the therapeutic dose is shown by the occurrence of toxicity in almost every case treated effectively. It has been generally accepted that toxicity is a necessary accompaniment of effective therapy, and the literature on this subject has been limited. The pharmacologic activities of the nitrogen and sulfur mustards have been excellently presented by Gilman and Philips in a classic article.[2] The therapeutic application as well as the toxic effects of nitrogen mustard depends on the formation of ethylenimonium in solution at body pH.



Methyl-bis (2 Chloroethyl) Amine (Nitrogen Mustard) — Ethylenimonium

This compound, which acts as an imonium cation, reacts, in a manner not clearly understood, with negatively charged molecules contained in the nuclei of living cells. The effect of this reaction closely resembles that of x-ray therapy. Nitrogen mustard has a selective effect for rapidly proliferating cells. Herein lies the basis for its palliative application against neoplastic disease. Likewise, since the hematopoietic system and the gastrointestinal tract contain the most rapidly proliferating cells in the body, they are more likely to reflect the toxic effect of therapeutic doses.

The most commonly recognized toxic effects of intravenous nitrogen mustard may be listed as: (1) local effects; (2) hematopoietic effects, and (3) gastrointestinal effects. The local effects usually result from inadvertent difficulties in administration of the drug. Extravasation of the drug causes pain, swelling, and usually sloughing of the subcutaneous tissue. Administration may also be followed by thrombophlebitis. The incidence of these complications has been greatly reduced by injection of the drug into the tubing of a freely running intravenous infusion.

Some effect on the hematopoietic system accompanies almost every therapeutic dose. The most common ones are lymphopenia and neutropenia, which usually occur seven to 14 days following treatment. These changes are rarely of an alarming degree and usually result in no ill effect to the patient. Mild

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anemia occasionally follows therapy. A few cases of thrombocytopenia, granulocytopenia and pancytopenia have been reported. Some of these have progressed to quite serious condition and, in a few cases, death.[3]

Nausea and vomiting usually occur two or three hours following administration of nitrogen mustard, and last 12 to 24 hours. This does not, as a rule, present any serious problem. Diarrhea and ulceration of the gastrointestinal tract are seen rarely. At least one death has been attributed to the toxic effect on the gastrointestinal tract.[4] Although numerous drugs have been used to counteract the gastrointestinal toxicity, we do not believe any of these to be better than simple sedation prior to administration of the drug. Reactions are minimized by injecting the drug at bedtime, following barbiturate sedation.

The purpose of this paper is to report a complication of nitrogen mustard therapy which has been poorly appreciated, as evidenced by the absence of any previous reports in the literature to the authors' knowledge.

Case Report

A 24 year old white male was admitted to Madigan Army Hospital on October 18, 1952, with a chief complaint of shortness of breath. He had enjoyed excellent health until two months prior to hospitalization, during which time he had lost 15 pounds in weight. He had a cough and had noted some lumps in his neck for three weeks. He was admitted to the hospital because of progressive dyspnea and dysphagia.

Physical Examination: Temperature, 98.6° F. The recumbent position produced severe shortness of breath. There was dullness to percussion over the upper mediastinum. A few moderately enlarged cervical, supraclavicular and axillary nodes were noted which were discrete, firm, nontender and movable.

The hematocrit was 45; hemoglobin, 15.4 gm.; white blood cells, 7,350, with a normal differential count. Chest x-ray revealed a large mediastinal mass.

The tentative diagnosis was Hodgkin's disease or lymphosarcoma. A biopsy of a cervical lymph node taken on October 20, 1952, was reported as lymphosarcoma. X-ray treatment to the mediastinum was started on the same date, with a dramatic improvement of symptoms within 24 hours. Chest x-ray on October 23 showed considerable decrease in the size of the mediastinal mass. During the course of therapy, pleural effusion developed on the right side. Aspiration of the fluid and cell block demonstrated lymphosarcoma cells. After further x-ray therapy the effusion disappeared, and chest x-ray on October 28 appeared normal. The patient became asymptomatic and gained weight. It was planned to irradiate the cervical and supraclavicular nodes as well as the site of pleural effusion, but because of the development of leukopenia, further x-ray therapy was withheld. The patient maintained his weight and remained asymptomatic until November 28. At this time he developed pain in the left lower chest posteriorly. Examination revealed tenderness to percussion over the ribs in this area and a few indurated, tender, purplish skin lesions. At this time large axillary and inguinal nodes were first noted. Because of the extensive involvement, it was decided that further x-ray therapy would not be adequate, and accordingly, 8 mg. of methyl-bis (2 chloroethyl) amine were given intravenously each night for four successive nights. Within three days he was again asymptomatic, with normal physical examination.

On January 7, 1953, evidence of skin metastases over the lower chest had recurred, and there was a sensation of fullness in the chest. Chest x-ray at this time revealed a slight increase in the width of the upper mediastinum and bilateral pleural

effusion. On January 8, 1953, 16 mg. of nitrogen mustard were given intravenously, and were repeated in 24 hours.

On January 10 the patient became oliguric and noted passage of yellow lumps in his urine. In view of the nausea and vomiting, it was thought that this might be due to dehydration, and a test infusion of 3,000 c.c. was given intravenously. This resulted in only a small urinary output. Hematuria with uric acid crystals raised the possibility of obstruction of the urinary tract due to precipitated uric acid. Because of persistent marked oliguria for another 24 hour period, and development of bilateral backache, emergency cystoscopy and retrograde urography were performed. Cystoscopy revealed the ureteral orifices to be completely blocked with yellow sand. Bilateral ureteral catheterization yielded a flow of sediment from each lower ureter, including a small calculus on the left side, located just within the orifice. X-ray showed a positive shadow in the right lower ureter, which disappeared after catheterization, and a 1 cm. radiolucent stone within the left renal pelvis (previous survey intravenous pyelograms on October 24 had been normal). Urinary pH was 5.0 from each kidney. Study of the sediment revealed uric acid crystals, and laboratory studies revealed the presence of uric acid. Tests for cystine were negative. On the day of cystoscopy the blood urea nitrogen was 72 mg. per cent, uric acid, 23.9 mg. per cent, and inorganic phosphorus, 10 mg. per cent. The ureteral catheters were retained in place and irrigated every two hours with an alkaline solution. The urinary output immediately increased, rising within 48 hours to amounts far exceeding the fluid intake, which was initially supplemented by intravenous solutions, including ⅙ M sodium lactate. Two days after catheterization vomiting had ceased and the patient was able to take an alkaline-ash, low-purine diet and 6 gm. of sodium bicarbonate daily. Urinary pH stabilized above 7.5 on this regimen. On January 15 the blood urea nitrogen was 35 mg. per cent and uric acid, 11.1 mg. per cent. A retrograde pyelogram on the left side the next day showed only residual roughening of the lower calyx. The catheters were then removed. Hyaluronidase, 500 units daily intramuscularly, was then given for one week to increase protective urinary colloids. After removal of the catheters the patient was ambulatory without complaints, and continued to have adequate urinary output, with pH of 7.5 or above. By January 19 the urine was negative on microscopic examination, and blood urea nitrogen and uric acid determinations were normal. Chest x-ray on January 23 showed the mediastinum to have returned to normal width and the bilateral pleural effusion to have disappeared.

Discussion

The therapeutic action of nitrogen mustard depends on its cytotoxic action through its reaction with nuclear substances. This reaction of necessity must result in breakdown of nucleoproteins. This leads to the formation of purines which are oxidized to uric acid in the body. As a result, the blood level of uric acid will be elevated, increasing the amount of uric acid excreted by the kidneys. If uric acid becomes supersaturated in an acid urine, crystallization will result, and the danger of obstruction of the urinary tract is impending. This case represents such a complication. The danger of this complication, as well as the frequency of nephrolithiasis and occasional occurrence of gout, has long been appreciated in the x-ray treatment of leukemia.[5, 6] A case of uremia complicating leukemia following treatment with triethylene melamine has recently been reported.[7] To the authors' knowledge, this complication has not been previously reported following nitrogen mustard therapy. The possibility of this complication must be stressed in the use of x-ray therapy and any of the chemotherapeutic cancer drugs,

which depend on cytotoxic action. In fact, this danger will be in direct proportion to the efficacy of the agent. Undoubtedly, oliguria and other complaints referable to the urinary system and the danger of impending renal shutdown have been overlooked because of the nausea and vomiting which are expected to accompany therapy with many of the cytotoxic agents.

The quantity of uric acid excreted in the urine will be directly related to the tumor mass, the sensitivity of the tumor, and the quantity of nitrogen mustard administered. The dosage schedule of nitrogen mustard in general use is 0.1 mg. per kilogram of body weight, administered daily for four doses. Some prefer to give 0.2 mg. per kilogram on two successive days, and a few have used even larger doses. This schedule is a rather crude one, based on body weight without consideration for tumor mass or sensitivity. Nevertheless, the large number of cases which have been treated successfully by this plan would indicate that it is a practical one. Obviously it is impossible to determine the tumor mass. The sensitivity of the tumor to nitrogen mustard can be estimated by observing the blood uric acid level and urinary excretion of uric acid following a small test dose. This response can be used in arriving at a safe therapeutic dose. This method is now being used in some centers in preference to the standard dose schedule.[8] Although this would appear to be an ideal method, it is not a practical one for general use. From a practical standpoint, it will be necessary to continue using the dose schedule based on body weight. It would seem reasonable to initiate treatment with the smaller dose of 0.1 mg. per kilogram body weight, and to resort to the larger doses only after the tumor becomes resistant.

The possibility of uric acid complications can be minimized by simple precautions to prevent the following two conditions which favor uric acid crystallization in the urinary tract: (1) a high concentration of uric acid in the urine; (2) an acid urine.

Determination of daily urinary output, and daily microscopic examination of the urine for hematuria and uric acid crystals, are simple measures which will give some warning that the development of this complication is imminent.

Adequate fluid intake during and following treatment is of extreme importance in preventing a concentrated urine and assuring an adequate urinary volume. Although many questions remain unanswered in the work on the solubility of uric acid in the human, it appears that the volume of the solution is the most important factor. Peters and Van Slyke state that if salt output per day remains equal, the urate that can theoretically be held in true solution in a 24 hour urine increases, not simply as the 24 hour volume, but as the square of the volume.[9] We believe that a fluid intake of at least 3,000 c.c. daily should be assured during the course of treatment, even if the oral intake must be supplemented by intravenous fluids, in order to maintain a urinary output of 2,000 c.c. daily. The infusion which is started to facilitate administration of the nitrogen mustard can be used to increase the total intake without additional discomfort to the patient.

The fluid loss from vomiting which may accompany therapy can be avoided, or at least reduced to an insignificant amount, by proper sedation with a barbiturate. We believe the dose of barbiturate should be more than that generally used, and should preferably be given parenterally. Vomiting can be prevented in most cases by the administration of 0.5 gm. of Amytal Sodium intramuscularly, 30 minutes before the injection of nitrogen mustard. The infusion should also

be started at that time to avoid awakening the patient when the nitrogen mustard is given.

One must not have a false sense of security when treating a young patient or one who is still in good physical condition. In fact, the ability of the normal kidney to concentrate efficiently makes the danger of this complication even greater in the young patient than in the elderly patient with some impairment of renal concentration.

Alkalinization of the urine by oral sodium bicarbonate, or by intravenous sodium lactate, should be a routine part of therapy. The importance of alkaline urine is illustrated by experimental work which shows the solubility of uric acid in urine to be increased from 8 mg. per 100 c.c. at pH 5 to 158 mg. per 100 c.c. at a pH of 7.0.[9] The efficacy of alkalinization appears to depend on the ability of urates to remain in a supersaturated or colloidal solution. Eight to 12 gm. of sodium bicarbonate daily, in divided doses, will usually produce an alkaline urine. Effective alkalinization can be assured by checking the urine with litmus or nitrazine paper. Again, the normal kidney, with its ability to excrete an acid urine, favors uric acid crystallization and increases the danger of this complication.

The recent use of hyaluronidase, with its ability to increase protective urinary colloids,[10] although not fully established, may prove it to be another valuable agent in preventing this complication.

A careful record of urinary output should be kept following treatment. If anuria develops in a patient following nitrogen mustard therapy, early ureteral catheterization should be attempted to confirm the diagnosis and to initiate treatment of the complication. If obstruction is present, this procedure may be life-saving.

The practical measures which have been discussed and which are recommended as routine orders for nitrogen mustard therapy may be listed as follows:

1. Record fluid intake and output.
2. Force fluids to 3,000 c.c. daily.
3. Sodium bicarbonate, 2 gm. every six hours.
4. Sodium Amytal, 0.5 gm. intramuscularly, 30 minutes prior to administration of nitrogen mustard.
5. Start 1,000 c.c. infusion of 5 per cent glucose in water intravenously, 30 minutes prior to administration of nitrogen mustard.
6. Daily urinalysis for blood and uric acid crystals.
7. Check urine pH four times a day.

Summary

1. The toxic effects of nitrogen mustard therapy have been reviewed.

2. A case has been presented of ureteral obstruction and renal calculi due to uric acid precipitation following nitrogen mustard therapy.

3. The explanation for the development of this complication, and some of the measures which may be of benefit in preventing and treating this complication, have been discussed.

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EDITORIAL

THE DIAGNOSIS OF PHEOCHROMOCYTOMA

"Careful consideration of the possible presence of a pheochromocytoma or a paraganglioma in every patient with hypertension, sustained or intermittent, must now be regarded as a diagnostic obligation. . . ." "Once thought rare, such tumors have recently been discovered to be the most common, surgically curable cause of high blood pressure. . . ." "The specificity, accuracy, convenience and safety of phentolamine (regitine) has established it as the testing agent of choice for routine use in screening all hypertensive patients."

These pronouncements, ably expressed by the DeCourcys, whose recent compilation [1] has been freely drawn upon in preparation of this editorial, summarize current opinion of the importance and diagnostic susceptibility of chromaffin tumors. It is rewarding to trace some of the steps which have brought us to our present position.

Historical Résumé

The first case of (presumable) pheochromocytoma was described in Germany by Fränkel [2] in 1886: bilateral adrenal tumors were found in an 18-year old girl with a year's history of attacks of headache, palpitation, dizziness, vomiting and pallor associated with a noncompressible pulse and retinal changes. The first description of the syndrome of paroxysmal hypertension in association with a chromaffin tissue tumor came from France in 1922: Labbé, Tinel and Doumer [3] found a pheochromocytoma above the left kidney in a 28-year old woman who had had attacks characterized by hypertension and numerous vasomotor and other symptoms and who died in an attack with acute pulmonary edema. The first correct clinical diagnosis made during life was recorded by Vaquez and Donzelot [4] also in France in 1926.

The first surgical cure was achieved in this country.[5] At the Mayo Clinic in 1927 a woman of 30 years was submitted to exploratory laparotomy because of increasing abdominal pain. She had a history of paroxysmal hypertension associated with many other symptoms and sometimes complicated by pulmonary edema. At operation a retroperitoneal tumor was removed and interpreted as a malignant blastoma; some years later reëxamina-

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tion of the tumor established its identity as that of a pheochromocytoma. The patient was cured and reported alive and well in 1952.

The first accurate preoperative diagnosis, followed by successful extirpation of the diagnosed tumor, was made by Pincoffs [6] in 1928. The diagnosis in this case was based entirely on clinical findings: "the abrupt rise in blood pressure, the evidence of peripheral vasoconstriction, the nervous tremulousness . . ., the violent heart action and the glycosuria all suggested an adrenalin effect."

The first step towards our current diagnostic methods by biochemical test was made by Fourneau and Bovet [7] in 1933 when they reported the marked anti-adrenergic action of piperidyl-methyl-benzodioxane. In 1937 the presence of a pressor agent in the blood of a patient during a hypertensive paroxysm due to a pheochromocytoma was first demonstrated by Beer, King and Prinzmetal.[8] Then in 1945 Roth and Kvale [9] introduced the provocative histamine test and two years later Goldenberg, Snyder and Aranow [10] introduced piperidyl-methyl-benzodioxane as a testing agent. Finally, in 1950 phentolamine (Regitine) was introduced by Grimson and his coworkers [11] and this substance has currently become the sheet anchor of diagnosis.

Clinical Features

The diagnosis may be shrewdly suspected, and sometimes diagnosed with confidence (as in the early cases of Vaquez and Donzelot and Pincoffs) from clinical features alone. It is important to realize that the "classical" picture of paroxysmal hypertension is seen in only a minority of cases. Most patients, probably about 70 per cent,[12, 13] have sustained hypertension with associated symptoms so similar to those of essential hypertension, benign or malignant, that diagnosis cannot possibly be made without a reliable chemical test. But though every hypertensive pattern may be associated with pheochromocytoma, it still holds true that it must be particularly suspected if the hypertension is paroxysmal. Other suspicious characteristics of the hypertension are wide fluctuations within the hypertensive range, or the

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finding of a postural fall in both systolic and diastolic blood pressures together with tachycardia when the patient stands.

Pheochromocytoma must be especially suspected clinically (1) if hypertension is present in a young person; if it first makes its appearance during pregnancy or the puerperium; or if a hypertensive crisis is precipitated by anesthesia, surgery or other trauma; (2) if the hypertensive patient has "attacks" or "spells" characterized by headaches, palpitations, tachycardia or bradycardia, precordial or abdominal pain, pallor or flushing, nausea, vomiting, blanching of the extremities, profuse sweating, blindness, aphasia or loss of consciousness; or (3) if the hypertension is associated with an elevated basal metabolic rate, other symptoms suggestive of hyperthyroidism, glycosuria or hyperglycemia.

An association to which attention has recently been drawn is that of pheochromocytoma with von Hippel-Lindau disease (angiomatosis retinae et cerebelli). Glushien and his colleagues [14] report two cases of pheochromocytoma associated with angiomatosis retinae, and refer to the well recognized, though not understood, relationship between chromaffin tumors and neurofibromatosis—about 5 per cent of reported pheochromocytomas have been associated with von Recklinghausen's disease.[15] They conclude that pheochromocytoma is mysteriously related not only to neurofibromatosis but also to von Hippel-Lindau disease, and perhaps to the other neurocutaneous syndromes (tuberous sclerosis and encephalotrigeminal angiomatosis). They believe that at least 10 per cent of patients with pheochromocytoma will be found to have some form of neurocutaneous disorder and that therefore stigmas of such disease in a hypertensive should arouse suspicion of pheochromocytoma.

The familial incidence of neurocutaneous syndromes is well documented. It is of interest that a familial incidence in pheochromocytoma has also been noted. The most remarkable instance of this to date is reported from the Mayo Clinic where bilateral pheochromocytomas were successfully removed from each of three siblings.[16]

In the physical examination the value of simple palpation should not be neglected as it has been estimated that about 14 per cent of all pheochromocytomas are palpable.[1] Cautious, gentle massage over the upper quadrants may cause a diagnostic rise in blood pressure; if this maneuver is undertaken, phentolamine must be available for immediate intravenous injection to forestall the development of a dangerous hypertensive crisis.

Differential Diagnosis

The syndrome produced by pheochromocytoma may well be mistaken for a number of other clinical entities; indeed, the DeCourcys are pleased to refer

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to it as the "great mimic." Because of the many symptoms common to both—tachycardia, heat intolerance, palpitation, loss of weight, increased appetite, flushing, sweating, nervousness, tremor, glycosuria, increased basal metabolic rate—pheochromocytoma may readily be confused with *hyperthyroidism*. To confound this confusion, pheochromocytoma may also cause swelling of the thyroid, exophthalmos, increase in protein bound iodine and a temporary response of the basal metabolic rate to antithyroid drugs. It is calculated that about 10 per cent of patients with pheochromocytoma are being treated for *diabetes mellitus* at the time the correct diagnosis is made. The easy confusion with *essential hypertension* has been referred to above. Other conditions which have been mistakenly diagnosed are *glomerulonephritis* [17] and other *renal lesions*,[18] *toxemia of pregnancy*, *eclampsia* and *psychoneurosis*. Pheochromocytoma has masqueraded as *gastrointestinal hemorrhage* [19] and *abdominal emergency*.[20, 21] In reverse, pheochromocytoma has been mimicked by such oddities as coarctation of the abdominal aorta [22] and renal cyst.[23]

It is thus clear that the responsibility of suspecting the diagnosis of pheochromocytoma may fall not only on the internist and cardiologist but also at times on the endocrinologist, gastroenterologist, dermatologist, neurologist, pediatrician, psychiatrist, ophthalmologist, abdominal or general surgeon, or urologist.

Epinephrine and Nor-Epinephrine (Arterenol)

Variations in the clinical picture produced by pheochromocytoma can to some extent be explained by the varying proportions of pressor substances liberated by the individual tumor. It was at first presumed that the hypertension and other symptoms of pheochromocytoma were caused by discharge of epinephrine into the circulation. Then Holton [24] and Goldenberg and his coworkers [25] demonstrated that pheochromocytomas contained a mixture of epinephrine and nor-epinephrine in varying proportions, with nor-epinephrine usually predominating. The six tumors first investigated contained from 53 to 97 per cent of nor-epinephrine. Goldenberg [26] investigated

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the effect of intravenous infusion of epinephrine and nor-epinephrine in man. The infusion of nor-epinephrine caused over-all vasoconstriction, with prompt rise in both systolic and diastolic blood pressures while cardiac output was little affected and the subjects were strikingly free from subjective symptoms. Infusion of epinephrine, on the other hand, led to over-all vasodilation with great increase in cardiac output and a rising systolic pressure accompanied by tachycardia, palpitations, anxiety and other symptoms; basal metabolic rate and blood sugar were also elevated by epinephrine, but were relatively unaffected by nor-epinephrine.

	Epinephrine	Nor-epinephrine
Vessels	vasodilator	vasoconstrictor
Blood pressure	systolic elevated	systolic and diastolic elevated
Cardiac output	marked increase	unaffected
Heart rate	tachycardia	bradycardia
Symptoms	++++	±
BMR	++	±
Blood sugar	++	±

The proportion of pressor amines, however, as determined by tumor analysis, has not always correlated neatly with the clinical manifestations. Goldenberg's studies [27] revealed that small tumors containing 90 to 97 per cent nor-epinephrine gave a syndrome mimicking essential hypertension without impressive metabolic features; when, on the other hand, the predominating catecholamine was epinephrine, the associated syndrome included hypertension, hypermetabolism, hyperglycemia and tachycardia. A surprising finding was that tumors containing large quantities of epinephrine sometimes presented a clinical picture indistinguishable from that of essential hypertension with normal heart rate, absence of metabolic disturbance and a negative response to piperoxan. This suggested that persistent hypertension in pheochromocytoma was not always due to the continuing presence of large quantities of catecholamines in the circulation; but that when significant amounts of these amines had been present for long periods, hypertension no longer requiring these circulating agents for its maintenance might be initiated. Further investigation along these lines may well throw light on the mechanism of essential hypertension.

Pharmacologic and Other Tests

Pharmacologic tests are the cornerstone of diagnosis. The substances used in such testing may be classified into two groups: *provocative* agents which induce a paroxysm of hypertension during a normotensive or nearly normotensive interval; and *adrenergic blocking* agents which cause a fall in blood pressure from its paroxysmal or sustained high level. Provocative agents introduced include histamine, tetraethylammonium chloride (TEAC, Etamon), tetraethylammonium bromide (TEAB), and methacholine (Mecholyl); adrenergic blocking agents include piperoxan (piperidyl-methyl-

[27] Goldenberg, M.: Adrenal medullary function, Am. J. Med. 10: 627, 1951.

benzodioxane, Benodaine, 933F), phentolamine (Regitine, C-7337) and Dibenamine.

The first pharmacologic substance to be introduced as a testing agent for pheochromocytoma was histamine[2]; in a patient with pheochromocytoma the intravenous injection of this substance causes an abrupt rise in blood pressure. Unfortunately this test is not entirely specific, and both false positive and false negative tests have been frequently recorded. Nor is the test without danger; a number of deaths have resulted from the hypertensive crises provoked by histamine in patients with pheochromocytoma. Now that phentolamine is available to control such crises, histamine can be more safely used and its main sphere of usefulness is in testing the patient with paroxysmal hypertension during a normotensive interval. Histamine base (0.025 mg. in 0.5 c.c. normal saline) is injected intravenously after baseline blood pressures have been obtained during a half hour rest period. After the injection, blood pressures are taken at minute intervals for 15 minutes; a sharp rise of more than 50 mm. systolic and 25 mm. diastolic is considered a positive test. In the absence of a pheochromocytoma a sudden drop in pressure is followed by a slight rise. Phentolamine must be at hand to control a hypertensive crisis, should one occur. If the patient is strongly suspected of having a pheochromocytoma, so that a marked and perhaps dangerous rise in pressure is to be anticipated, phentolamine may be given prophylactically to prevent a dangerous hypertensive crisis. An oral dose of 25 to 50 mg., given an hour before the histamine injection is made, will avert an extreme rise in pressure, but intravenous phentolamine should still be held in readiness.

Of the other test substances used, Dibenamine has had a short and stormy career; it has rapidly proved itself to be too inaccurate and too dangerous for practical use. Piperoxan has enjoyed a longer and less tarnished career, though it too has now been virtually discarded by many authorities as less accurate and more toxic than phentolamine. In selected cases, however, it still remains a useful diagnostic tool in confirmation of equivocal phentolamine tests.

Phentolamine has rapidly established itself as the testing agent of choice. It has several notable advantages over piperoxan: (1) it is almost free of unpleasant side reactions; (2) it is notably more accurate; (3) it is much easier to administer—one person can carry out the entire test as an office procedure; and (4) it does not cause the alarming rise in blood pressure that piperoxan sometimes causes in the essential hypertensive.

After determining the basal level of blood pressure, 5 mg. of phentolamine dissolved in 1 c.c. of sterile distilled water is injected either intramuscularly or intravenously; in children 1 mg. is given intravenously or 3 mg. intramuscularly. When the intramuscular route is employed, blood pressure determinations are made at five minute intervals for 30 minutes; when the drug is administered intravenously, readings are taken at 30 second intervals for three minutes and then every minute for 7 additional minutes.

In a patient with pheochromocytoma and associated hypertension, the typical response is a prompt fall in blood pressure of more than 35 mm. systolic and 25 mm. diastolic. The only undesirable effects of intravenous phentolamine have been moderate tachycardia, and occasionally flushing, dizziness or weakness; the intramuscular dose has caused only moderate tachycardia. As recently as 1952 Gifford and his associates [28] were able to say that no false negative reactions had been recorded with phentolamine given intravenously. With intramuscular administration a number of false negatives have been reported, and so the intravenous route is considered preferable.

To avoid false positive responses certain precautions must be taken; thus it is important to be certain that the patient has taken no sedative or narcotic for at least 24 hours preceding the test. The use of antihypertensive agents must be discontinued the previous day, or, in the case of thiocyanate, for 4 to 6 days prior to testing. It is also important to know that in the presence of severe uremia phentolamine may cause a marked fall in blood pressure in hypertensive disorders other than pheochromocytoma.[28, 29] If these prerequisites are faithfully met, the DeCourcys consider that "false positive responses to the phentolamine test are so rare as to be practically negligible." If the criteria of a positive test as outlined above, i.e., a systolic fall of at least 35 mm. and diastolic of at least 25 mm., are strictly adhered to, many of the so-called "false positives" so far reported are eliminated. If, however, one of the criteria used by Gifford and his colleagues (namely, a fall in pressure to below 140/90 regardless of how little above that level the baseline pressure was) is accepted, the incidence of false positives increases. Blood pressure readings must be made with extreme accuracy as declines of as much as 30 mm. systolic and 20 mm. diastolic have been frequently observed in hypertension due to causes other than pheochromocytoma.

Superior as phentolamine appears to be, no one drug should be regarded as infallible and all equivocal responses should be confirmed by testing with other pharmacologic agents. At the Mayo Clinic [30] it is the practice to use histamine for patients whose resting blood pressure is less than 170/110, and phentolamine (or piperoxan) if the resting blood pressure is greater than this.

A method of diagnosis from estimation of urinary catechols was introduced by Engel and von Euler [31, 32] in Scandinavia. Epinephrine and other catechol derivatives are normally excreted in the urine in conjugated form, the normal epinephrine-nor-epinephrine output per day being 20 to 40 μg.

[28] Gifford, R. W., Roth, G. M., and Kvale, W. F.: Evaluation of new adrenolytic drug (Regitine) as test for pheochromocytoma, J. A. M. A. **149**: 1628, 1952.

[29] Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S.: Use of piperoxan and Regitine as routine tests in patients with hypertension, J. A. M. A. **146**: 1383, 1951.

[30] Sprague, R. G., Kvale, W. F., and Priestley, J. T.: Management of certain hyperfunctioning lesions of the adrenal cortex and medulla, J. A. M. A. **151**: 629, 1953.

[31] Engel, A., and von Euler, U. S.: Diagnostic value of increased urinary output of noradrenaline and adrenaline in pheochromocytoma, Lancet **2**: 387, 1950.

[32] von Euler, U. S.: Increased urinary excretion of noradrenaline and adrenaline in cases of pheochromocytoma, Ann. Surg. **134**: 929, 1951.

In 6 cases of pheochromocytoma they found quantities 10 to 50 times this amount. They concluded that by estimating the total output of norepinephrine and epinephrine in the urine a reliable diagnosis of pheochromocytoma could be obtained. These findings were confirmed in two cases by Goldenberg.[27] If a simplified method of catecholamine measurement becomes available, urinary estimations promise to afford a most valuable diagnostic method.

X-ray studies may prove of value in some cases. Plain x-ray of the abdomen, laminagraphy, or pyelography may rarely give evidence of an adrenal tumor but are seldom conclusive. In experienced hands perirenal air insufflation or the injection of air into the retroperitoneal space are maneuvers more likely to afford useful evidence in selected cases.

Smithwick and his coworkers [33] stressed the diagnostic value of a normal cold pressor test in differentiating pheochromocytoma from essential hypertension in which a normal test is rare. But because of the variability in response to this test by all types of hypertensive patients, more recent opinion is inclined to regard this test as of only limited diagnostic value. Moreover, although a "normal" response is the rule in pheochromocytoma, occasionally the cold pressor test may precipitate a hypertensive crisis.

Pheochromocytoma is not so rare as it was formerly thought to be. In 1940, 103 cases had been reported [34] and by 1950 the number had increased to 270.[33] It has recently been stated that more than 1,000 deaths from pheochromocytoma occur annually in the United States.[1] The importance of diagnosing pheochromocytoma where it exists thus deserves stressing. With the advent of phentolamine it has become relatively easy and safe to exclude this type of tumor and all hypertensives deserve to have this simple test performed. If diagnosis is achieved before irreversible damage is done, results of surgery are gratifying and life-saving.

H. J. L. M.

[33] Smithwick, R. H., Greer, W. E. R., Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma: a discussion of symptoms, signs and procedures of diagnostic value, New England J. Med. **242**: 252, 1950.

[34] Brunschwig, A., and Humphries, E.: Excision of pheochromocytoma following near fatal attack of paroxysmal hypertension, J. A. M. A. **115**: 355, 1940.

REVIEWS

Enzymatic Concept of Anaphylaxis and Allergy and the Rôle of Eosinophils in Anaphylactic Reactions Related to Hormonal Alterations. By Z. Z. GODLOWSKI, M.D. (Cracow), Ph.D. (Edin.), M.R.C.P. (Edin.), Research Fellow of the Carnegie Trust, Edinburgh; foreword by A. MURRAY DRENNAN, M.D., F.R.C.P.E., F.R.S.E., Professor of Pathology, University of Edinburgh. 120 pages; 22.5 × 14.5 cm. E. & S. Livingstone, Ltd., Edinburgh and London; available in U. S. A. from the Williams and Wilkins Co., Baltimore. 1953. Price, $3.50.

The above titled monograph consists of three chapters dealing with phases of the anaphylactic phenomenon. The first attempts an explanation on the basis of enzyme activity, a second discusses hormonal involvement in the reaction and the third deals with the rôle of eosinophil cells.

In building up the thesis for the enzyme concept the author introduces new concepts of sensitization and its resulting reaction. On page 1 he says "the anaphylactic phenomenon should be regarded rather as resulting from *the failure of the antigen-antibody reaction*," a statement which is not only bold but completely unorthodox. Dr. Godlowski then proceeds "to give a brief description of the nature and mode of action of antigen and antibody and of the mechanism of sensitization and anaphylactic shock" as he conceives it. The outline of the hypothesis is best described in his own words as follows: "Sensitization is a condition in which toxic enzymes appear in the cells involved as a result of antigenic action. Antigen may therefore be described as any substance which when introduced into the animal organism, whether orally or parenterally, is able to induce the formation of (1) a toxic enzyme system in the cells liable to be sensitized and (2) specific antibodies in the tissues concerned. These two fundamental features of antigen are not necessarily coupled with each other, i.e., the production of specific antibodies may take place in an organism in which sensitization has not occurred and vice versa."

Another, so far as I am aware, novel idea is presented in the statement that antigenic proteins may be incorporated into the host-cell and "may or may not alter the whole character of these cells. Furthermore, this physiopathological state may be transmitted to the next generation according to the Mendelian law."

The author develops the concept of enzyme activity by the assumption of several proteolytic enzymes, those normal to the organism which hydrolyze protein, antigenic or non-antigenic, to the level of non-toxic catabolites, then there are specific proteolytic enzymes (antibodies) which act only on antigen and reduce it to non-toxic substances and finally a third type, "specific proteolytic toxic enzymes" whose formation constitutes the basic phenomenon of anaphylactic sensitization and the products of whose activity create the toxic catabolites of the shock reaction.

Naturally the analogy of peptone shock is used to support the author's thesis of toxic protein split products but nowhere does one find, in the first chapter, any new evidence as a result of his own work or that of any other research scholar. In short then, this chapter of the book is acceptable only as an interesting presentation of pure hypothesis without the merit of factual support for the presence of the toxic enzymes or their toxic catabolites.

In the second chapter on hormonal involvement the author assumes that the chemical stress created by anaphylactic proteolysis mobilizes the pituitary-adrenal response and releases corticosteroids of many sorts. Certain of these disrupt the lipoprotein molecules resulting in partial hydrolysis and hence the production of toxic basic protein catabolites. The beneficial effect of the adrenal steroids which is the outstanding contribution to therapy in allergic disease is barely and inadequately noted.

The final chapter deals with the rôle of eosinophils in anaphylaxis. The author has carried out interesting investigations and supports his histologic findings with excellent color plates; but again the discussion becomes largely speculative. He regards eosinophils as "carriers of antigens" and cites them as "examples of isolated cells which have developed a new function—that of synthesizing foreign protein." In fact, the author states that "if large numbers of these cells (eosinophils) are destroyed their antigenic proteins may be liberated in sufficient amounts to precipitate an anaphylactic reaction" although he believes this rare.

It is to be hoped that the author will continue his studies to develop support for his theses. This is not the first time that enzymes have been discussed in relation to immunity and anaphylaxis. I am reminded here of the publication of Sevag in 1945 entitled "Immuno-Catalysis," a book replete with experimental facts indicating the relationship of enzyme and antigen.

Godlowski's book is not one that adds to our knowledge and is not one for the immature student of immunology but it may afford interesting discussion and speculation among the seasoned immunologists and enzymologists.

ROBERT A. COOKE, M.D.

Cancer (Experimental and Clinical). Section XVI of Excerpta Medica. Editors: R. VAN DAM and W. VAN WESTERING. 700 to 800 pages a year (published monthly). 24.5 × 17.5 cm. 1953. Excerpta Medica, N. V., Amsterdam (The Netherlands).

Excerpta Medica, now in its seventh year of publication in the field of comprehensive medical abstracting, offers to the medical world a new section devoted to the world's literature on all phases of cancer research and therapeutics. This section, XVI, began with vol. 1, no. 1, July 1953. Vol. I which consists of 6 monthly issues from July to Dec. 1953 is $5.00 (or the equivalent in local currency). Vol. II (1954) and succeeding volumes will consist of 12 monthly issues and will be priced at $10.00/yr. The Editorial Board is composed of members of high international standing in their various fields of cancer research and therapeutics. Generous grants authorized by the National Cancer Institute of the U. S. Public Health Service and the American Cancer Society, Inc. attest to the value of these publications.

The world's literature on the subject of cancer has grown tremendously in the last two decades and will increase more rapidly in years to come. It is impossible for the busy investigator and clinician to keep up with the large number of articles being published. An abstract service such as the Cancer Section of Excerpta Medica makes it possible to obtain in a short time the essentials of the important articles, and determine the ones giving information desired by the reader for more complete study.

The articles are well chosen and condensed. All phases of the cancer problem are covered—General Theories, Statistics, Experimental, Pathology, Metastasis, Diagnostics, Therapy, etc. The anatomical classification also aids materially in finding subject matter.

This Section on Cancer is a must for all libraries and research laboratories, as well as investigators and clinicians. It is a much needed addition to the world's literature.

GRANT E. WARD

Gastric Cancer. By ALFRED H. IASON, M.D., Attending Surgeon, Adelphi Hospital. 316 pages; 17.5 × 26 cm. Grune and Stratton, New York. 1953. Price, $7.50.

Dr. Iason is a surgeon, anatomist, and author who has attempted to summarize the cumulative literature and to express his views gained from experience in the field of gastric cancer. He has aimed this present work at students and clinicians, and

has used an approach which is so fundamental that one would assume the novices in medicine to constitute the bulls-eye of his target.

His basic, all-inclusive teaching technic at first may slow down the reader and then bore him by apparently unnecessary repeating and overlapping, especially in the chapters devoted to the anatomy and histology of the esophagus and stomach. However, once the reader has gotten into the clinical chapters, it becomes obvious that this book contains a tremendous amount of carefully collected and sifted material which is very well arranged and carefully indexed.

The chapters devoted to the preparation for and surgical therapy of gastric cancer begin well, but too soon bog down into a detailed, step-by-step, type of lesson in various operative technics. The chapter on anesthesia provides similar instructions with several paragraphs describing the chemical and pharmacologic properties of each of the commonly used anesthetic agents as well as the step-by-step technics for their administration. The discussion of postsurgical treatment is excellent, and the section on postoperative complications is lengthy and detailed. In essence there is a mass of excellent material in this book. The technic of presenting each aspect of the gastric cancer problem in such detail from the basic science level through the clinical level reminds one of the "do it yourself" kit instructions with which many young homemakers are currently familiar. This feature detracts from the excellence of the work and provides instruction in subordinate subjects, for example anesthesia, which may be obtained more properly from other sources.

W. C. E.

Aspects of the Psychology of the Tuberculous (A Psychosomatic Medicine Monograph). By GORDON F. DERNER, Ph.D. 119 pages; 15.5 × 24.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1953. Price, $3.50.

A clinical psychologist presents a descriptive and somewhat superficial study of some attitude and personality factors in a group of tuberculous patients. At least one section of this monograph, the detailed report of attitudes and feelings of the investigated group, obtained by interview, may be of considerable interest to practitioners concerned with the alleviation of the characteristic apprehension and depressive feelings of tuberculous patients. The implication is that, because of the patient's fears related to the disease, the most effective treatment approach should be psychotherapeutic in orientation. On several scores, however, the possible significance of the research is diminished; by an unfortunate choice of subjects (a highly atypical population); by a questionable selection of measuring instruments (some of which are clearly inapplicable to the individuals being appraised); by the scanty and indifferent analysis of data (largely non-integrated); by a lack of appropriate controls, and in general by a somewhat inadequate research design. Research proposals born of a clinical setting are ofttimes overambitious, and so it is with this project, which attempts to do much and—except as a descriptive document—achieves little.

The subjects are 32 young adult patients of the tuberculosis division of a county hospital in New York. Of the patients chosen, 12 were medically trained (either as nurses or physicians). The population appears to be a highly educated, ethnically and socially unrepresentative group of whom only 10 are male. Seen individually, each patient was given a controlled interview, a number of personality questionnaires and tests, and two projective diagnostic instruments. The bulk of the monograph is concerned with analyses, sometimes unwieldy and over-elaborate, of data yielded by these devices.

One rather intriguing aspect of the study is the investigation of the phenomenon of *spes phthisica*, the euphoric hopefulness of recovery which is often reported as occurring in patients with tuberculosis. Based on the results of an exceedingly brief

written questionnaire, it is here suggested that this euphoria is not found to any significant degree. It is to be regretted, however, that a more comprehensive and meaningful exploration was not attempted; the present findings should not be interpreted as unequivocally rescinding this particular medical term.

H. A. R.

Diseases of the Liver, Gallbladder and Bile Ducts. 3rd Ed. By S. S. LICHTMAN, M.D., F.A.C.P. 1357 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1953. Price, $22.00.

Since the second edition of this book, it has expanded from 1135 pages to 1357 and now appears as a two-volume work in place of the single volume in editions one and two. It is a most comprehensive undertaking and represents a tremendous task on the part of the author to assemble the massive data now available and to keep it within a reasonable size. On the subject of size, perhaps one might suggest that, since the discussion of the liver is the principal endeavor of the author and since there are so many good treatises on the subject of diseases of the gall bladder and bile ducts, perhaps Part 2 of Volume 2 entitled "Diseases of the Gall Bladder and Biliary Passages" and representing pages 1159 to 1315 might well be considered as a separate book. This is suggested for two reasons. First, the field of liver diseases is expanding rapidly and no doubt the size of the book will increase in future editions; the smaller amount of space devoted to the gall bladder and biliary passages is not absolutely essential to the present treatise although it may, under other circumstances, be considered an integral part of a discussion on biliary system diseases. In comparing the three editions, there is every indication that the author has tried to correct the criticisms voiced in former reviews and that whatever redundancies remain must be considered by him as essential in such a monumental undertaking.

The book pursues its discussion in a careful, studious, rational way, taking up first the structure of the liver, then the normal and pathological physiology of the liver and biliary structures, entering then into a discussion of the clinical pictures, the diagnostic tests and including an evaluation of the multitudinous liver function tests and their interpretations. Disease entities are discussed in detailed fashion including many ramifications into diseases, frequent and rare, associated with abnormalities of the liver. Such subjects as the "Protective Functions of the Liver" are illuminating and give rise to many ideas which could lead to further research. An explanation of peptic ulcer associated with jaundice in animals is mentioned in passing only to raise the question immediately in the reader's mind that such an association is notably less, if at all, impressive in the human. As one would hope and expect in such an all-inclusive compilation, efforts are made to elucidate many ideas related to hepatic coma; a condition about which much must be learned and in which therapy is often so ineffectual.

There is no question that the use of liver function tests has recently gotten out of hand but in this volume, the indications for the tests, their interpretations and limitations are carefully and helpfully presented. Liver biopsy is discussed briefly as well as the use of the peritoneoscope in the diagnosis of liver disease. Perhaps the author may consider more fully in future editions a comparison of the physiologic data obtained by liver function tests with the anatomic and histologic data obtained by biopsy. Many are hopeful that in this area of correlation may be found an understanding of the mechanism and time pattern of the development of liver disease.

The discussion of hepatitis is full and modern. Many of the new concepts regarding the treatment of hepatitis and cirrhosis are fully described. Such difficult problems as ascites in cirrhosis, its medical and surgical treatment, are satisfactorily discussed. The subject of portal hypertension is summarized clearly and a reasonably

full discussion is available of the surgical approach to this problem. The position of antibiotics in the treatment of liver conditions is made fairly clear.

In summary, the author has made available a complete work on diseases of the liver and the biliary system in general. In each revision there is a clear effort to exclude conflicting data but in his desire to present all views, there is bound to be some overlapping. Considering that the two volumes have 220 illustrations and 3 color plates and that since the last edition in 1949 so many new ideas, advances and research in the field of liver disease have made necessary this third edition, the increase in size of the present book is understandable. It is worth repeating that as handy as it is to have the additional, commendable passages on "Diseases of the Gall Bladder and Bile Ducts," the size of the book could be kept within limits if the latter were considered a separate work. With their exhaustive number of references the volumes serve as an up-to-the-minute discussion on biliary system diseases and should, therefore, be recommended and considered an essential part of the physician's library as well as an invaluable aid to the student. Finally, the volumes are a credit to the author in his admirable attempt to keep us abreast of a field of endeavor in which he has been especially interested for so many years and to which he has been one of the important contributors.

S. M.

A Textbook of Pathology: An Introduction to Medicine. 6th Ed. By WILLIAM BOYD, M.D., Dipl. Psych., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S.(C), LL.D (Sask.), D.Sc. (Man.), M.D. (Oslo), F.R.S.(C). 1,024 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1953. Price, $12.50.

The student of medicine today more than ever is startled all too frequently by drastic changes that take place in the sum of medical knowledge.

In the writing of any textbook, brevity and usefulness are difficult to achieve. In the writing of a textbook of Pathology, the task is herculean, if not impossible. Choosing exhausted—or neglected—concepts for deletion and new promising ideas from the glutted medical press requires judgment and foresight that few possess. Armed with both, the author attempts to revivify this book by including numerous subjects of recent interest. A motley and imposing list of new material is mentioned in the preface, and accorded brief treatment in the text. The sketchy accounts do little to improve this textbook as a reference work.

The author of necessity arbitrarily limits the content of many sections in an attempt to present extensive and involved subjects in an assimilable form. To the student's delight, controversial subjects are over-simplified and presented as dogma.

The reader of this, as of all previous editions, cannot help appreciating the charming style of the author and by it is constrained to read further.

This reviewer, although adversely critical of certain features of this book, considers it a useful volume. Over-simplification, brevity and avoidance of controversy help the medical student to gain a point of view in pathology. A pleasing glimpse to start might entice him to take in the whole scene.

D. L. R.

Stedman's Medical Dictionary. 18th revised edition. Edited by NORMAN B. TAYLOR, V.D., M.D., F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lon.); and ALLEN E. TAYLOR, D.S.O., M.A. 1605 pages; 17 × 25.5 cm. The Williams and Wilkins Company, Baltimore. 1953. Price, $11.50.

This latest edition of an old standby is considerably larger than its predecessor; this is thanks to the addition of nearly six hundred illustrations (many of them rather grotesque) and several thousand new terms. A new feature is that most of the

anatomical terms which had been listed in previous editions in their Latin forms have been translated into their more commonly encountered English equivalents and have been arranged in the form of Tables.

In quality as well as in size and price this dictionary now rivals its two competitors.

H. J. L. M.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

An Atlas of Pelvic Operations. By LANGDON PARSONS, M.D., Professor of Gynecology, Boston University School of Medicine, etc.; and HOWARD ULFELDER, M.D., Assistant Clinical Professor of Gynaecology, Harvard Medical School, etc.; illustrated by MILDRED B. CODDING, A.B., M.A., Surgical Artist, Department of Surgery, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts. 231 pages; 29.5 × 36 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $18.00.

Clinical Disorders of the Heart Beat. By SAMUEL BELLET, M.D., Director, Division of Cardiology, Philadelphia General Hospital, etc. 373 pages; 26.5 × 17.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $8.50.

Clinical Management of Behavior Disorders in Children. By HARRY BAKWIN, M.D., Professor of Clinical Pediatrics, New York University, etc.; and RUTH MORRIS BAKWIN, M.D., Associate Professor of Clinical Pediatrics, New York University, etc. 495 pages; 23 × 17.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $10.00.

Doctors, People, and Government. By JAMES HOWARD MEANS, M.D. 206 pages; 21.5 × 14.5 cm. 1953. An Atlantic Monthly Press Book. Little, Brown and Company, Boston. Price, $3.50.

Expert Committee on Leprosy: First Report. World Health Organization Technical Report Series No. 71. 28 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

Expert Committee on Mental Health: Third Report. World Health Organization Technical Report Series No. 73. 38 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

Gourmet Cooking for Cardiac Diets. By FLORENCE FIELD; introduction by HAROLD FEIL, M.D. 350 pages; 22 × 15 cm. 1953. The World Publishing Company, Cleveland. Price, $3.50.

Joint UN/WHO Meeting of Experts on the Mental-Health Aspects of Adoption: Final Report. World Health Organization Technical Report Series No. 70. 19 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 15 cents.

The Management of Pain, With Special Emphasis on the Use of Analgesic Block in Diagnosis, Prognosis, and Therapy. By JOHN J. BONICA, M.D., Director, Department of Anesthesia, Tacoma General and Pierce County Hospitals, etc. 1,533 pages; 26.5 × 18.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $20.00.

Modern Clinical Psychiatry. 4th Ed. By ARTHUR P. NOYES, M.D., Superintendent, Norristown State Hospital, Norristown, Pennsylvania, etc. 609 pages; 24.5 × 15.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $7.00.

Nursing: A Survey of Recent Legislation. (Reprint from the *International Digest of Health Legislation* **4**: 461–498, 1953.) 35 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

Peripheral Nerve Injuries: Principles of Diagnosis. 2nd Ed. By WEBB HAYMAKER, M.D., Chief, Neuropathology Section, Armed Forces Institute of Pathology, Washington, D. C., and BARNES WOODHALL, M.D., Professor of Neurosurgery, Duke University School of Medicine, Durham, North Carolina. 333 pages; 24.5 × 16 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $7.00.

A Primer of Cardiology. 2nd Ed. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc. 339 pages; 24 × 16 cm. 1953. Lea & Febiger, Philadelphia. Price, $5.50.

Respiratory Diseases and Allergy: New Method of Approach. By JOSEF S. SMUL, M.D. 80 pages; 21 × 14 cm. 1953. Medical Library Company, New York. Price, $2.75.

Shock and Circulatory Homeostasis: Transactions of the Second Conference, October 19, 20, and 21, 1952, Princeton, N. J. Edited by HAROLD D. GREEN, M.D., Professor of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. 275 pages; 23.5 × 15.5 cm. 1953. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.75.

Spatial Vectorcardiography. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc.; J. A. ABILDSKOV, M.D., Instructor in Medicine, Tulane University School of Medicine, etc.; and JAMES A. CRONVICH, M.S., Professor of Electrical Engineering, Tulane University College of Engineering, New Orleans. 173 pages; 24 × 15.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $5.00.

World Directory of Medical Schools. 220 pages; 24.5 × 16 cm. 1953. World Health Organization, Geneva. Price, $4.00.

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses

The College program of Postgraduate Courses continues in the same successful pattern as in recent years. The excellence of the instruction, the variety and timeliness of courses and their distribution among different medical centers and geographic locations, are the responsible factors. The Committee on Postgraduate Courses has been particularly effective in appointing as directors men who are preëminent teachers, who know the interests of the particular group of doctors served by these courses, and who give most liberally of their time in supervising each course.

Courses 1, 2, 6, 7 and 8 were all oversubscribed, resulting in many applicants being turned away. This was especially true of Course Number 8 where probably more applicants had to be turned away than could be accepted, this after the maximal number was increased from 25 to 50. The registration figures at the time of the preparation of this News Note, November 3, for each course, were as follows:

Number of Registrants	*Course*
101	No. 1, CARDIOVASCULAR DISEASES: New York University College of Medicine; Charles E. Kossmann, M.D., F.A.C.P., Director.
92	No. 2, PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE: Duke University School of Medicine; Eugene A. Stead, Jr., M.D., F.A.C.P., Director.
72	No. 3, INTERNAL MEDICINE: University of Chicago School of Medicine; Wright R. Adams, M.D., F.A.C.P., Director.
60	No. 4, CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia; Bernard J. Alpers, M.D., F.A.C.P., Director.
24	No. 5, PRESENT DAY THERAPY AND ITS PHYSIOLOGICAL BASIS: University of Utah College of Medicine; Maxwell M. Wintrobe, M.D., F.A.C.P., and Louis S. Goodman, M.D., Co-directors.
38	No. 6, SEMINARS IN INTERNAL MEDICINE: Vanderbilt University School of Medicine; Rudolph Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., F.A.C.P., Co-directors.
32	No. 7, THE NEWER BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO CLINICAL PROBLEMS: University of Wisconsin Medical School; William S. Middleton, M.D., M.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Co-directors.
53	No. 8, BALLISTOCARDIOGRAPHY: Johns Hopkins Hospital; Benjamin M. Baker, Jr., M.D., F.A.C.P., Director.
472 Total *	

Tentative Schedule, Postgraduate Courses, Spring, 1954

The Committee on Postgraduate Courses and the Board of Regents will announce the exact and definite schedule of courses for the winter and spring of 1954 in the next issue of this journal, but the following is the tentative schedule:

* Incomplete.

CLINICAL GASTRO-ENTEROLOGY: Louisiana State University School of Medicine, New Orleans, La.; Gordon McHardy, M.D., F.A.C.P., Director; March 15–20, 1954.

SELECTED SUBJECTS IN INTERNAL MEDICINE: Columbia University College of Physicians and Surgeons, New York, N. Y.; Franklin M. Hanger, M.D., F.A.C.P., Director; one week, date to be determined.

ELECTROCARDIOGRAPHY: Wayne University College of Medicine, Detroit, Mich.; Gordon B. Myers, M.D., F.A.C.P., Director; one week, date to be determined.

DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Leo H. Criep, M.D., F.A.C.P., Director; May 17–21, 1954.

HEMATOLOGY: Northwestern University, University of Illinois and University of Chicago, Chicago, Ill.; Howard L. Alt, M.D., F.A.C.P., Director; Leon O. Jacobson, M.D., F.A.C.P., and Louis R. Limarzi, M.D., F.A.C.P., Co-directors; one week, date to be determined.

NEOPLASTIC DISEASES AND RADIOISOTOPES: Memorial Center for Cancer and Allied Diseases, New York, N. Y.; Cornelius P. Rhoads, M.D., F.A.C.P., and Rulon Rawson, M.D., Co-directors; one week, date to be determined.

INTERNAL MEDICINE: University of California Medical School, San Francisco, Calif.; Stacy R. Mettier, M.D., F.A.C.P., Director; June 14–18, 1954, the week immediately preceding the AMA Annual Meeting.

RADIOISOTOPES: Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; June 14–18, 1954.

Post-Convention Seminar in Mexico City

Following the Annual Session of the American College of Physicians at Chicago, April 5–9, 1954, a Post-Convention Tour and Seminar will be conducted to Mexico City via the American Air Lines. DC-6 planes offering the utmost in comfort and reliability will be used. The party, limited to 100 individuals, will leave Chicago at 10:40 a.m., Saturday, April 10, arriving that evening in Mexico City in time for dinner. Headquarters will be at Hotel Geneve. A series of lectures and presentations is being arranged at the National Institute of Cardiology of Mexico and at the Hospital de Enfermedades de la Nutricion through the instrumentality of Dr. Ignacio Chavez, College Governor for Mexico, and Dr. Salvador Zubiran, F.A.C.P., Professor of Internal Medicine at the National University School of Medicine of Mexico. It will afford an opportunity to visit some of the more important medical institutions in Mexico City, and to observe at first hand their facilities. These scientific programs will be arranged during the mornings of Monday, Tuesday and Wednesday, April 12, 13 and 14.

Sunday, April 11, will be devoted to a motor tour to the Floating Gardens, Xochomilco, where the Mexican people love to cruise the canals in their "canoas." Sunday afternoon will be free to visit the bullfight, if desired, or other forms of sight-seeing or entertainment can be selected. After the seminars on Monday, Tuesday and Wednesday, the afternoons will be devoted to shopping, motor tours about the city and residential sections, a visit to the National Palace to see the Calendar Stone, the former home of Emperor Maximilian in fashionable Chapultepec Park, the Church of Guadalupe, the most sacred shrine in the Republic, Teotihuacan, the Home of the Gods, Pyramids of the Sun and Moon, the highest artificial mounds in North America, the Temple of Quetzalcoatl, Desert of Lions, San Angel, Pedrigal and other suburban districts. There always will be opportunities made for shopping.

On Thursday and Friday, April 15 and 16, there will be a two-day motor tour to Taxco and Cuernavaca. Taxco is a dream village cradled by mountains and dominated by the cathedral. Cuernavaca is a picturesque old city, where the Aztec kings had their summer homes. Now official and diplomatic Mexico and others of wealth and fashion have their residences here.

On Friday, April 17, there will be an all day motor tour by a mountain road of great beauty passing the mighty snow capped peaks of Ixtaccihuatl and Popocatepetl, lush green valleys, Indian villages and markets, Cholula with its Aztec pyramid and then lunch at Puebla, the "Rome of Mexico." That evening a farewell dinner will be given at Hotel Geneve, and on Sunday morning the group will depart by plane returning to their respective homes in the States.

The price of the tour and seminar is to be $386.15, covering almost all expenses on the regular program. A slight additional charge is made for single-room occupancy. The tour will be in charge of Mr. Leon V. Arnold, 36 Washington Square, W., New York 11, N. Y., who has conducted many other Post-Convention Tours and Cruises so successfully for the College. Mr. Arnold will in due course furnish full details to all members of the College, and others may obtain same on request. It is believed that the expenses of a physician attending this medical seminar may be deducted on his Income Tax account, but that would not apply to other members of his family.

A.C.P. Regional Meetings

Since January 1, 1953, Regional Meetings of the College have been conducted in Eastern Pennsylvania, Colorado, Virginia, Delaware, Nebraska, Southern California, New Hampshire-Vermont-Maine, Kansas, Southern Illinois, West Virginia, North Dakota, Arkansas-Oklahoma, Western Pennsylvania, Western New York, Kentucky, Ohio, Montana-Wyoming, Southwestern Area (Alabama, Florida, Georgia, South Carolina, and Cuba), Pacific Northwest (Alberta, British Columbia, Idaho, Oregon, Washington), Arizona, New Jersey, Utah, Puerto Rico, Midwest (Illinois, Indiana, Iowa, Minnesota, Wisconsin), North Carolina and Michigan.

Without exception, attendance has been gratifying, programs have been excellent, and the social features have been especially attractive. Officers and Regents of the College have in almost all instances accepted invitations as guest speakers on the programs and, more particularly, at the dinner meetings in the evening.

Regional Meetings already scheduled for 1954 include the following:

EASTERN PENNSYLVANIA, Philadelphia—January 15
MARYLAND-D. C., Baltimore—January 16
COLORADO, Colorado Springs—January 22–23
SOUTHERN CALIFORNIA, Riverside—February 13–14
VIRGINIA, Richmond—February 25
KANSAS, Topeka—March 19
SOUTHERN ILLINOIS, Peoria—March ?
NORTH DAKOTA, Bismarck—September 11
NEW ENGLAND, Hartford—October 22

American Trudeau Society Offers Teaching-Resident Fellowships

The American Trudeau Society, Medical Section of the National Tuberculosis Association, provides a limited number of fellowships to promote the training of clinicians, medical teachers and administrators in the field of tuberculosis and related

pulmonary diseases. The awards are open to citizens of the United States for work within this country. Preference is given to candidates not more than thirty years of age who have the degree of Doctor of Medicine.

Awards are made for graduate study in internal medicine, with emphasis on diseases of the chest, in an approved hospital. Fellows are expected to assume some responsibility for the teaching of chest diseases to undergraduate medical students. The American Board of Internal Medicine will accept one such year as a part of the prerequisite training for certification.

Stipends are determined by individual circumstances and may vary from $2,400 to $3,200 per annum, paid on a monthly basis. They are made for one year. Not more than two renewals will be considered. Fellowship applications are considered at meetings of the Committee on Medical Education of the American Trudeau Society in October and April or May; to receive consideration at these meetings they must be received by September 1 or April 1. Appointments may begin on any date determined by the Board at the convenience of the applicant, who may elect the hospital in which he wishes to study and the staff member who will supervise his work.

Further particulars concerning these fellowships may be obtained from The Director of Medical Education, American Trudeau Society, c/o Henry Phipps Institute, 7th & Lombard Sts., Philadelphia 47, Pa.

Continuation Course in Neurology

The University of Minnesota will present a Continuation Course in Neurology for general physicians and specialists from January 25 to 30, 1954, in the Center for Continuation Study at Minneapolis. Diagnosis and management of the more commonly-met neurological disorders will be stressed. There will be a number of distinguished guest physicians on the faculty from other institutions. The course will be directed by Dr. A. B. Baker, Professor and Director of Neurology of the University of Minnesota. Additional information can be obtained from Dr. Robert B. Howard, Director of the Department of Continuation Medical Education, University of Minnesota Medical School, Minneapolis 14, Minn.

New Journal, Radiation Research

The Radiation Research Society will initiate a new bi-monthly journal known as "Radiation Research" starting February, 1954. The managing editor will be Dr. Titus C. Evans, State University of Iowa College of Medicine. In this journal will be published original articles dealing with all phases of Radiation Research to promote the integration of the disciplines of physics, chemistry, biology and medical research as they are concerned with the effects of radiation on matter. The journal will be published by the Academic Press, Inc., 125 E. 23rd St., New York 10, N. Y.

Certifying Board in Nutrition

A certifying Board to establish standards of qualification of persons as specialists in human nutrition and to certify as such, persons who comply with the standards, has been established by persons and organizations interested in the practice of the science of nutrition, according to the American Medical Association. The principal purpose of this board is to certify non-physician specialists, and the Board is not related to the various American Medical Specialty Boards, the Advisory Board for Medical Specialties or the Council on Medical Education and Hospitals of the American Medical Association. However, physicians can be certified if they wish and are

able to meet the requirements. Otto A. Bessey, University of Texas College of Medicine, Galveston, Texas, is the Secretary-Treasurer.

Coming Examinations by Certifying Boards

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Written Examinations: Selected places, Jan. 15, 1954. This is the only written examination which will be given during 1954.

Oral Examinations: Indianapolis, Ind., Dec. 4–6, 1953,
Washington, D. C., Feb. 19–21, 1954,
Des Moines, Iowa, March 19–21, 1954,
New York, N. Y., May 1–3, 1954,
San Francisco, Calif., June 25–27, 1954,
Chicago, Ill., Oct. 8–10, 1954,
New Haven, Conn., Dec., 1954.

The American Board of Radiology, B. R. Kirklin, M.D., Secretary-Treasurer, 102 Second Ave., S.W., Rochester, Minn.

Spring Examinations: Cincinnati, Ohio, April 26–30, 1954.

Fall Examinations: Washington, D. C., Sept. 13–17, 1954.

New Jersey American College of Physicians Regional Meeting

The Eighth Annual Regional Meeting of the American College of Physicians for New Jersey was held at Trenton, November 5, 1953, under the Governorship of Edward C. Klein, Jr. Dr. Raymond E. Miller, F.A.C.P., Trenton, was Chairman of the Committee on Arrangements, and Drs. Louis F. Albright, F.A.C.P., Asbury Park, and Frank J. Altschul, F.A.C.P., Long Branch, were Co-Chairmen of the Program Committee.

Speakers on the scientific program and their subjects were: Dr. Isabel M. London (by invitation), Highland Park, "Infection and Peripheral Vascular Disease in Diabetes"; Dr. William J. Snape, F.A.C.P., Camden, "Duodenal Ulcer as an Etiological Factor in Jaundice"; Dr. Clifford K. Murray, F.A.C.P., Ventnor, "Recent Developments in Plasma Expanders"; Dr. Margaret Hay Edwards (Associate), Trenton, "Carbohydrate Metabolism and Peptic Ulcer"; Dr. Charles E. Lyght, F.A.C.P., Rahway, "Hydrocortisone in Medical Practice"; Dr. Edward Weiss, F.A.C.P., Philadelphia, "Functional Factors in Heart Disease."

A reception and banquet were held in the evening with Dr. Thomas J. White, F.A.C.P., Jersey City, acting as Toastmaster. Dr. Lemuel C. McGee, F.A.C.P., College Governor for Delaware, and Dr. Jeter A. Isely, Assistant Professor of History at Princeton University, were the official guest speakers, their speeches being, respectively: "Proposal Procedure and Credentials Committee Problems" and "The Assault on Iwo Jima." Dr. George Morris Piersol, M.A.C.P., Philadelphia, Dr. Thomas M. McMillan, F.A.C.P., Governor for Eastern Pennsylvania, Philadelphia, and Mr. Edward R. Loveland, Executive Secretary of the College, were special guests. This was an especially successful meeting with an attendance estimated at 150.

Virginia Section, American College of Physicians

The Annual Business Meeting of the Virginia Section of the College was held on October 20, 1953, at Roanoke, Va., during the 3-day meeting of the Medical So-

ciety of Virginia. Cocktails and luncheon preceded the meeting. It was determined to hold the winter scientific session at Richmond on Thursday, February 25, 1954.

Officers elected for 1954 include: Chairman of the Regional Meeting, Dr. John Powell Williams, Richmond; Secretary, Dr. James F. Waddill, Norfolk. Among guests at this business meeting were Dr. Robert L. King, F.A.C.P., President of the American Heart Association, Seattle, Wash.; Dr. Claude Forkner, F.A.C.P., Professor of Clinical Medicine, Cornell University Medical School, New York. Dr. Walter B. Martin, F.A.C.P., President-Elect of the American Medical Association, and for many years a Regent of the College, addressed the meeting. There were 55 members and 2 guests present.

Eighth Congress, Italian Medico-Sportive Federation

The Eighth Congress of the Italian Medico-Sportive Federation will meet at Trieste during the spring or early summer of 1954. Two days will be devoted to scientific discussions and one day to the Convocation of the National Meeting. Subjects under discussion will include Infectious Diseases in Connection with Sportive Activities, and Muscular Strain. Contributions on these subjects are solicited by Federazione Medico-Sportiva Italiana, Foro Italico, Rome, Italy.

Dr. Francis M. Pottenger, M.A.C.P., Celebrates 84th Birthday and 50th Anniversary of the Founding of the Pottenger Sanatorium

More than 600 friends and former patients of Dr. Francis M. Pottenger attended a huge Garden Party at the Sanatorium at Monrovia, Calif., on September 27, 1953, not only to celebrate the 84th birthday of Dr. Pottenger, but also the 50th Anniversary of the founding of the Pottenger Sanatorium. Guest and ex-patients came from scores of cities. Dr. Edward F. Kupka, F.A.C.P., Chief of the Bureau of Tuberculosis Control of the California Department of Public Health, delivered the principal address describing the early efforts of Dr. Pottenger, who is the first physician on the Pacific Coast to devote his whole time to the study and treatment of tuberculosis. For many years there has been an Annual "Homecoming" at the Sanatorium each year to celebrate Dr. Pottenger's birthday and to pay homage to him. In 1953 this became a more significant occasion not only because of his advancing age, but also to commemorate the Golden Anniversary of the Sanatorium.

Dr. Pottenger is one of the earliest Fellows of the American College of Physicians and served on its Board of Regents for many years. He was President in 1932–33, and is still a valued counsellor. He is the author of a great many books dealing with diseases of the chest and is one of the great American pioneers in this field.

Prominent Members of the College Appointed to National Advisory Arthritis and Metabolic Diseases Council

Dr. Maurice C. Pincoffs, M.A.C.P., Baltimore, Md., and Dr. Howard A. Rusk, F.A.C.P., New York, have recently been appointed to serve on the National Advisory Arthritis and Metabolic Diseases Council, National Institutes of Health, Department of Health, Education, and Welfare. A former President of the College, Dr. Pincoffs has for many years been Editor of the *Annals of Internal Medicine* and has been Professor of Medicine at the University of Maryland School of Medicine and College of Physicians and Surgeons since 1922. Dr. Rusk is Chairman of the Department of

Rehabilitation and Physical Medicine of New York University College of Medicine and has gained an international reputation for his achievements in the field of rehabilitation.

Dr. Conley H. Sanford, F.A.C.P., College Governor for Tennessee, has retired as Chief of the Staff of John Gaston Hospital and as Chief of the Division of Medicine of the University of Tennessee College of Medicine. He will continue as Professor of Medicine and as a private practitioner.

Capt. Gerald W. Smith, (MC), USN, F.A.C.P., for the past three years Commanding Officer of the U. S. Naval Hospital at Philadelphia, has been transferred to a similar capacity at the Naval Hospital on Treasure Island, San Francisco, Calif. He has been succeeded at Philadelphia by Capt. Courtney G. Clegg, (MC), USN, who was transferred from the Naval Hospital at Bremerton, Wash.

International Medical Assembly

The International Medical Assembly of the Interstate Postgraduate Medical Association of North America was held at Chicago, November 2–5, 1953. Dr. Jonathan C. Meakins, M.A.C.P., Montreal, was installed as President.

University of Buffalo Schools of Medicine and Dentistry Dedicate Capen Hall

Distinguished physicians and dentists from England, Canada, and many parts of the United States participated in scientific symposia at the University of Buffalo, December 11–12, 1953, in connection with dedication exercises for the Samuel P. Capen Hall, the new building for the Medical and Dental Schools of the University of Buffalo. The building was recently completed at a cost of $4,500,000. Funds were provided by contributions by individuals and corporations. Among the participants in the symposia were: Dr. Charles H. Best, co-discoverer of insulin, Professor of Physiology and Director of the Banting-Best Institute at the University of Toronto; Dr. Robin R. A. Coombs, Assistant Director of Research, Institute of Pathology, University of Cambridge, England, well known for the "Coombs Test" for the detection of Rh sensitization in new born babies; Dr. Stanley E. Dorst, President of the Association of American Medical Colleges and Dean of the University of Cincinnati College of Medicine; and Dr. Maynard K. Hine, President of the American Association of Dental Schools and Dean of the University of Indiana School of Dentistry.

Dr. Samuel P. Capen, after whom the new building is named, was the guest of honor. He is Chancellor Emeritus of the University of Buffalo and served as Chancellor from 1922 to 1950.

Following the dedication exercises on December 11, a number of separate symposia were conducted. Dr. J. Roscoe Miller, F.A.C.P., President of Northwestern University, was a participant in the symposium on medical and dental education. Dr. Jerome W. Conn, F.A.C.P., Professor of Internal Medicine at the University of Michigan Medical School, Dr. Thaddeus S. Danowski, F.A.C.P., Renziehausen Professor of Research Medicine at the University of Pittsburgh School of Medicine, and Dr. Herbert Pollack, F.A.C.P., Chief of the Metabolic Clinic at Mt. Sinai Hospital, New York City, were participants in the symposium on Parenteral Nutrition.

Albert Weinstein, M.D., F.A.C.P., Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, addressed the Tri-State Medical Society at Shreveport, La., September 30–October 1, 1953, on the subject, "Radioactive Iodine in the Treatment of Thyrotoxicosis."

Malpractice Protection

Members of the American College of Physicians are well aware of the fact that in the past few years, insurance companies have year by year increased the premiums for malpractice protection. The rates in some localities are exceptionally high. Almost 3,000 members of the College, answering a questionnaire a year or so ago, believe that the College should take some action in providing its members with this type of insurance, believing that the character of the College membership would warrant lower rates and would thus discourage the trend toward ever-increasing premium charges.

If members of the College will more completely organize into a tight group, there is small doubt but that their malpractice problem can be very actively handled. For this reason the Committee on Insurance of the College arranged a Plan of Group Malpractice Insurance which was offered to the members in January, 1953.

Upon questioning members who have not accepted this Group Plan, many and varied reasons were given. Among the most common were: Savings not great enough to make it worth trouble to change; we get our coverage through a good patient and would hesitate to change; we have not had time to study the Plan offered.

Through our representatives, The Association Service Office, there will be presented a new contract and a new schedule of rates. The new rates are slightly higher in some areas in the low protection brackets, but there is a substantial savings in every instance in the higher protection brackets. Also, coverage is being given up to $100/300,000, and for electric shock therapy. This new schedule is thought to be of decided advantage to the majority of members, especially in view of the fact that one employee will be automatically covered in the base premium at no extra charge.

The new agreement provides for an automatic reduction in rates, if the experience of our group is as good as is to be expected. However, to secure this reduction in rate, at least 50% of the College members must be insured under this Plan by January 1, 1955. Applications have been sent to every member. It is hoped that each member will send in his application for malpractice protection, to become effective when his present policy expires.

Other associations have on occasion tried some plans which later failed because of lack of support by its members. We do not want our Plan to fail because it offers superior coverage at favorable rates. It is hoped that the College Plan will grow year by year, providing protection at ever-decreasing rates, because the College group is definitely a preferred one. It is strongly recommended that all members coöperate in making this Malpractice Group Insurance Plan a full success and a continuing benefit to every member.

Dr. Frank B. Queen, F.A.C.P., Professor of Pathology at the University of Oregon Medical School, has been made President-Elect of the American Society of Clinical Pathologists, the largest group of specialists in pathology in the United States, numbering some 1,700 members.

Dr. Queen will assume office in September, 1954, at the International Congress of Clinical Pathologists meeting in Washington, D. C.

Dr. Wayne Gordon, F.A.C.P., Billings, Mont., succeeded to the Presidency of the American Association of Medical Clinics, and Dr. Arthur H. Griep (Associate), Evansville, Ind., was reëlected Secretary-Treasurer at the annual session of the Association, held in Chicago, Oct. 9–11. Dr. Edwin P. Jordan, F.A.C.P., is the Executive Director and maintains his official headquarters at Charlottesville, Va.

Dr. M. C. Carlisle, F.A.C.P., Waco, was chosen President-Elect of the Texas Pediatric Society at its annual meeting in Corpus Christi, Oct. 2–3. He had previously served four years as Secretary of the Society.

Dr. William D. Paul, F.A.C.P., Iowa City, has recently been named President-Elect of the American Congress of Physical Medicine and Rehabilitation. Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., was elected Treasurer, and Vice Presidents include Dr. Howard A Rusk, F.A.C.P., New York, and Dr. Alvin B. C. Knudson, F.A.C.P., Washington, D. C.

Dr. Frederick K. Herpel, F.A.C.P., West Palm Beach, was installed as President of the Florida Medical Association at its recent annual meeting in Hollywood.

Dr. Thomas P. Murdock, F.A.C.P., Meriden, Conn., former College Governor for Connecticut, was recently appointed by the Honorable John Lodge, Governor of Connecticut, to serve as physician member of a commission to study the establishment of medical, dental and veterinary colleges in New England. Established by the General Assembly earlier this year, the commission will collaborate with groups conducting similar studies in other New England states.

Dr. Howard P. Lewis, F.A.C.P., Portland, Ore., a Regent of the College, was recently elected President of the North Pacific Society of Internal Medicine at its fall meeting at Harrison Hot Springs, B. C., Can. Dr. Edwin G. Bannick, F.A.C.P., Seattle, Wash., was elected to the Vice Presidency, and Dr. Clarence C. Pearson, F.A.C.P., also of Seattle, was chosen Secretary-Treasurer. Dr. Roger H. Keane, F.A.C.P., Portland, Ore., was made a member of the Executive Committee.

Dr. Mildred C. J. Pfeiffer, F.A.C.P., Philadelphia, was elected President of the Pennsylvania Public Health Association at the annual meeting held in Wilkes-Barre, Oct. 9.

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, received the degree of Doctor of Medicine (Honoris Causa) from the medical faculty of the Ludwig Maximilian University of Munich, Germany, on the occasion of his seventieth birthday. Dr. Wiggers had studied at the University in 1912 and had been a pupil of Otto Frank in the physiological institute.

Dr. Walter C. Alvarez, F.A.C.P., Chicago, on behalf of the American Gastroenterological Association, recently awarded the Julius Friedenwald Medal to Dr. Burrill B. Crohn, F.A.C.P., New York.

Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., who was recently appointed by President Eisenhower to the National Advisory Committee of the Selective

Service System, has also been made a member of the Health Resources Advisory Committee, the appointment being made by the Director of Defense Mobilization.

Dr. James Alexander Lyon, F.A.C.P., Washington, D. C., was awarded by the Ohio University Alumni Association a Certificate of Merit "in recognition of distinguished attainments in the fields of internal medicine and cardiovascular diseases which reflect credit on his alma mater and are viewed with satisfaction by the Alumni Association."

Dr. William C. Menninger, F.A.C.P., Topeka, Kans., was honored recently by the Alumni Association of Cornell University Medical College when he was given an Award of Distinction "in recognition of his notable achievements in the teaching and practice of psychiatry, whose life and work have brought honor and acclaim to his medical college."

Dr. Elliott P. Joslin, M.A.C.P., Boston, delivered the Sixth Annual Harvard Lecture on "Diabetes, Today and Tomorrow" at the University of Colorado Medical Center, Denver, Oct. 30.

Dr. Walter C. Alvarez, F.A.C.P., Chicago, and Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., were two of the guest speakers at the annual session of the New York State Academy of General Practice, held in New York City, Oct. 26–28. In addition to participating in round-table discussions, Dr. Alvarez spoke on "Our Neurotic Population" and "Geriatric Neuroses," and Dr. Stieglitz discussed "Patients, 70 Years and Older."

Dr. Donovan C. Browne, F.A.C.P, New Orleans, was one of the guest speakers at the annual meeting of the Southwestern Medical Association, meeting in Tucson, Ariz., Oct. 29–31. His presentations included "Controversial Problems in Management of Peptic Ulcer," "Postgastrectomy Dumping Syndrome" and "Management of Chronic Ulcerative Colitis."

At the recent yearly meeting of the National Association for Mental Health, held in Cleveland, Dr. Walter H. Baer, F.A.C.P., Peoria, Ill., was the discussion leader for workshops on "Activities of Mental Health Associations Related to Psychiatric Aids."

Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., and Dr. William H. Sebrell, Jr., F.A.C.P., Bethesda, Md., were among the distinguished guests at the 47th Annual Meeting of the Southern Medical Association, held in Atlanta, Ga., Oct. 26–29. Dr. Martin discussed "Federal Medicine, Its Impact on the Medical Care of the American People," and Dr. Sebrell explained "Research in the Clinical Center of the National Institutes of Health, Public Health Service."

Drs. James H. Currens, F.A.C.P., James A. Evans, F.A.C.P., and Conger Williams (Associate), all of Boston, were among the out-of-state speakers at a Symposium on Cardiovascular Diseases, held during the annual meeting of the Vermont Heart Association, Burlington, Oct. 26–30, in coöperation with the Vermont Heart Commission and the University of Vermont College of Medicine.

Dr. Sara M. Jordan, F.A.C.P., Boston, addressed the dinner meeting of the Maine Medical Association at its fall clinical session in Bangor, Oct. 26. Her topic was "Digestion, Diet, and Doctors." Dr. Jordan also was one of the panel members at the Annual Postgraduate Day of the Sixth Councilor District of the Ohio State Medical Association. The program was presented Oct. 28 in Canton.

Dr. Harold Brandaleone, F.A.C.P., New York, discussed "Medical Aspects of Accident Prevention" before the Ohio State Safety Conference in Cleveland, Sept. 15.

Dr. Franklin A. Kyser, F.A.C.P., Chicago, spoke on "Preservation of Renal Function" at the Fifth Annual Medical and Surgical Symposium of the Raleigh (N. C.) Academy of Medicine on Oct. 16.

Dr. Russell L. Cecil, F.A.C.P., New York, was among the guest speakers at the 79th Annual Session of the Oregon State Medical Society, which convened in Portland, Oct. 14–17. His subjects were "The Treatment of Chronic Arthritis," "Old Age and the Vices," and "Influenza and the Common Cold."

Drs. George E. Burch, Jr., F.A.C.P., New Orleans, and Lewis Dexter, F.A.C.P., Boston, were among the guest speakers at the Annual Symposium on Cardiac Disease sponsored by the Los Angeles County Heart Association in October. In addition to presenting papers, they joined Dr. George C. Griffith, F.A.C.P., Pasadena, Calif., in a round-table discussion of valvulotomy for mitral stenosis, selection of patients, rôle of cardiac catheterization, and preoperative and postoperative care and results.

Dr. William Dameshek, F.A.C.P., Boston, delivered the weekly lecture on Oct. 31 at the Hartford (Conn.) Hospital, using "Idiopathic Thrombocytopenic Purpura" as his topic.

Dr. George T. Harrell, Jr., F.A.C.P., Winston-Salem, N. C., was the guest speaker at the First Annual Clinical Seminar sponsored by the Bluefield (W. Va.) Sanitarium, Oct. 2. His subject, presented at the banquet that evening at the Bluefield Country Club, was "Myxedema."

Among the guest speakers at the annual scientific assembly of the Connecticut Chapter of the American Academy of General Practice were Drs. Joseph B. Vander Veer, F.A.C.P., and Edward Weiss, F.A.C.P., Philadelphia. Their respective topics were "Diagnosis and Treatment of Cardiovascular Emergencies" and "Diagnosis and Treatment of Psychosomatic Disorders." The meeting was held in Hartford, Oct. 8.

Dr. Clyde H. Kelchner, F.A.C.P., has recently returned after a two and one-half months tour of 13 countries in Europe and Africa, being a delegate of the American Rheumatism Association to the International Rheumatism League Congress at Geneva and Zurich. He was also an Official Observer for the United States Committee at the World Medical Association Meeting at the Hague.

Dr. Frederick L. McDaniel, F.A.C.P., Richmond, Va., has recently accepted a position with the Central Inspection Board of the American Psychiatric Association. He formerly had served for four years as Assistant to the Commissioner of the State Department of Mental Health and Hospitals.

Dr. Marcus W. Newcomb, F.A.C.P., Browns Mills, N. J., was the guest of honor at a recent testimonial dinner in recognition of his 50 years as a practicing physician and his 34 years as Director of the Marcus W. Newcomb Hospital for Chest Diseases, New Lisbon.

Dr. Norman L. Cressy, F.A.C.P., formerly of Northampton, Mass., has recently been appointed Director of Medical Education at Uncas-on-Thames Sanatorium, Norwich, Conn.

Dr. Harold A. Lyons, F.A.C.P., formerly Assistant Professor of Medicine, Georgetown University School of Medicine, was recently appointed Associate Professor of Medicine at the State University of New York College of Medicine at New York City.

Effective November 1, Dr. Geoffrey William Rake (Associate), New York City, became Research Professor of Microbiology in Medicine at the University of Pennsylvania School of Medicine, and Research Professor of Microbiology in Medicine at the University's School of Veterinary Medicine.

Drs. Benjamin Manchester, F.A.C.P., Washington, D. C., Lee Douglas van Antwerp, F.A.C.P., Chicago, and Theodore R. Van Dellen, F.A.C.P., Chicago, were among those to receive fellowships in the American Medical Writers' Association at the Tenth Annual Meeting of the society in Springfield, Ill., on Sept. 23. The fellowships are awarded "in recognition of high qualifications, personal and professional and of established standing as a medical writer, journalist or publisher."

Dr. George R. Herrmann, F.A.C.P., Professor of Medicine at the University of Texas, Galveston, recently presented three papers on a program of medical conferences at the Medical School of University of Puebla, Mexico.

Dr. Oscar Swineford, Jr., F.A.C.P., Clinical Professor of Medicine at the University of Virginia School of Medicine, Charlottesville, addressed the Philadelphia Allergy Society, Oct. 28 on "Background Observations on the Bacterial Allergy Problem."

Dr. Louis H. Bauer, F.A.C.P., New York City, Past President of the American Medical Association, delivered the Sixth Judd-Plummer Memorial Lecture in Rochester, Minn., Oct. 2. His topic was "The Impact of Current Socio-Economic Trends upon American Medicine."

Meeting in Baltimore Oct. 21, the Maryland Academy of General Practice heard Dr. Alexander Marble, F.A.C.P., Boston, and Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, discuss, respectively, "Late Complications of Diabetes: Prevention and Treatment" and "The Management of Cardiac Failure."

Dr. O. Spurgeon English, F.A.C.P., Philadelphia, and Dr. Norman Reider, F.A.C.P., Berkeley, Calif., were two of the principal speakers at a special three-day Institute on Emotions and the Female Reproductive System, being held in Topeka, Kans., Dec. 10–12. In addition to participating in panel discussions, Dr. English spoke on "Psychosomatic Aspects of Dysmenorrhea, Pre-Menstrual Tension, Amenor-

rhea and Leukorrhea," and Dr. Reider spoke on "Psychosomatic Aspects of Frigidity." Dr. William Rottersman (Associate), was General Chairman of the Program Committee. Other participants included Dr. Lewis L. Robbins, F.A.C.P., Dr. Nathaniel Uhr, F.A.C.P., and Dr. Cotter Hirschberg (Associate), all members of the staff of the Menninger Foundation. The Institute was presented at the Winter Veterans Administration Hospital under the auspices of the University of Kansas School of Medicine and the Menninger Foundation.

Four members of the College contributed to the success of the Twelfth Annual New England Postgraduate Assembly held in Boston, November 2–4, under the General Chairmanship of Dr. Frank P. Foster, F.A.C.P., Boston. Dr. Charles A. Ragan, Jr., F.A.C.P., New York, spoke on "Complications of and Contraindications to the Use of ACTH and Cortisone"; Dr. Eugene H. Drake, F.A.C.P., Portland, Maine, discussed "Modern Pharmacopoeia for Heart Disease"; Dr. Bram Rose, F.A.C.P., Montreal, Can., read a paper concerning "Management of Progressive Asthma," and Dr. Gordon M. Meade (Associate), Saranac Lake, N. Y., gave a presentation entitled "Medical Management of Tuberculosis."

Dr. Ragan also gave the Third Annual Ralph Pemberton Memorial Lecture, entitled "The Pathologic Physiology of Bone and Joint Disease," in Philadelphia, Oct. 29. The lecture was sponsored by the Philadelphia Rheumatism Society and the Eastern Pennsylvania Chapter of the Arthritis and Rheumatism Foundation.

Dr. William B. Leaman, F.A.C.P., Professor of Medicine in the Woman's Medical College of Pennsylvania, spent the period of Oct. 25–Nov. 20, on an extensive medical speaking tour of the United States. He addressed the Oklahoma City Clinical Congress, the King County (Seattle, Wash.) Medical Society, meetings of the medical faculty of the University of Southern California and the College of Medical Evangelists at Los Angeles, the medical personnel of the U. S. Naval Hospital at Corona, Calif., and participated in seminars at the University of Indiana School of Medicine at Indianapolis. Additionally, he participated in medical programs at Portland, Ore., San Francisco and Santa Barbara, Calif., and Paducah, Ky.

At the annual meeting of the State Medical Society of Wisconsin, held in Milwaukee Oct. 6–8, Dr. Paul L. Shallenberger, F.A.C.P., Sayre, Pa., discussed "Lesions of the Lower Colon." Other out-of-state speakers and their topics included Dr. Charles K. Friedberg, F.A.C.P., New York, "Electrolyte Disturbances of Heart Disease" and Brig. Gen. Elbert DeCoursey, F.A.C.P., Washington, D. C., "The Pathology of Hemorrhagic Fever." Dr. Oliver P. Kimball, F.A.C.P., Cleveland, led a round-table discussion on "Epilepsy in Relation to Inheritance."

Dr. Edgar A. Hines, Jr., F.A.C.P., Rochester, Minn., speaking on "Medical Aspects of Peripheral Vascular Diseases," addressed the annual meeting of the Gulf Coast Clinical Society, held in Mobile, Ala., Oct. 15–16. Dr. Tinsley R. Harrison, F.A.C.P., Birmingham, participated in a clinico-pathologic conference.

Drs. Henry B. Kirkland, F.A.C.P., and Harry E. Ungerleider, F.A.C.P., New York, were among the participants in a panel discussion on "Systolic Heart Murmurs" that was part of the annual meeting of the Association of Life Insurance Medical Directors, held in New York City, Oct. 14–16.

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, talked on "Post Cholecystectomy Syndrome" and "Diseases of the Gastro-intestinal System" at the Fourth Annual Com-

bined Meeting of the Vermont State and New Hampshire Medical Societies. Dr. Joseph F. Ross, F.A.C.P., Boston, discussed "Immunohematologic Diseases" before the Section on Internal Medicine. Dr. Paul K. French, F.A.C.P., Burlington, Vt., is President of the Vermont Society, which was the host for the meeting, held Oct. 4–6, in Manchester.

Dr. Harold W. Lovell, F.A.C.P., New York, and Dr. William Likoff, F.A.C.P., Philadelphia, were among the guests at the annual meeting of the Medical Society of Delaware, held in Wilmington, Oct. 12. Dr. Lovell discussed "Abuse of the Barbiturates" and Dr. Likoff spoke on "Treatment of Cardiac Emergencies."

Dr. Israel Davidsohn, F.A.C.P., Chicago, was one of the principal speakers at the Thirty-Second Annual Meeting and Nineteenth Seminar of the American Society of Clinical Pathologists, Chicago, Oct. 13–16. Immediate Past President of the Society, Dr. Davidsohn talked on "Indications and Contraindications for Whole Blood and Its Various Fractions." Dr. Thomas H. McGavack, F.A.C.P., New York, collaborated in the presentation of "The Chemical Determination of Urinary Steroids," and Dr. Edwin F. Hirsch, F. A. C. P., Chicago, acted as moderator of a Symposium on Surgical Pathology.

Under the Co-chairmanship of Dr. Sidney Schnur, F.A.C.P., Houston, Tex., the Sixth Industrial Health Conference, presented by the Houston Chamber of Commerce, was held Oct. 1–3, in Houston. In addition to the speakers reported in last month's issue of this journal, the following members of the College also made presentations: Rear Admiral Lamont Pugh, (MC), USN, F.A.C.P., Washington, D. C., "Noise, Noxious or Nice"; Dr. Arthur J. Vorwald, F.A.C.P., Saranac Lake, N. Y., "Medical Aspects of Air Pollution"; Dr. Robert L. King, F. A. C. P., Seattle, Wash., "American Heart Association and Industry"; and Dr. Robert E. Eckardt (Associate), Linden, N. J., "A Medical Research Program in Industry."

The Twenty-First Annual Assembly of the Omaha Mid-West Clinical Society was held at Omaha, Nebraska, October 26–29, 1953. Dr. Donald J. Wilson, F.A.C.P., presented a scientific exhibit on "Problems in the Treatment of Common Dermatoses, Including Therapeutic Dermatitis," and presented a paper on the same subject. Dr. F. Lowell Dunn, F.A.C.P., with others, presented a scientific exhibit on Vectorcardiography. Among other local Fellows participating in the program were Drs. Henry J. Lehnhoff, Jr., Adolph Sachs, Eugene E. Simmons, John F. Gardiner, Frank R. Barta, Meyer Beber, F. W. Niehaus, Ernest L. MacQuiddy, Arthur M. Greene, and Edmond M. Walsh. Also, the following Associates made contributions: Drs. Donald J. Bucholz, John D. Hartigan, and Clifford H. Hansen.

Guest speakers and their subjects were: Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., "Emotional and Mental Illness in General Practice," "Men in Their Fifties," and "Middle Age, Menopause and Mental Disease"; Dr. Grace A. Goldsmith, F.A.C.P., New Orleans, La., "Recent Advances in Nutrition of Importance to the Physician," "Differential Diagnoses of Anemias and New Methods of Therapy," and "The Management of Protein Deficiency Syndromes"; Dr. William S. Hoffman, F.A.C.P., Chicago, Ill., "Principles of Potassium Metabolism," "Diagnosis and Management of Clinical Dehydration," "Liver Function Tests in Diagnosis and Treatment of Hepatitis"; Dr. Lewis M. Hurxthal, F.A.C.P., Boston, Mass., "Differential Diagnosis of Menopausal Syndrome," "Diagnosis and Treatment of Adrenal Disorders," "Endocrine Problems in Adolescence," and "The Iodine Stained Vaginal Smear and Its Use in Office Practice."

Members of the committees of the Society include Drs. Joseph D. McCarthy, F.A.C.P., College Governor for Nebraska, Willis D. Wright, F.A.C.P., Ben Slutzky, F.A.C.P., Harold N. Neu, F.A.C.P., William E. Kelley (Associate), and Albert V. Murphy (Associate).

Dr. Herbert Pollack, F.A.C.P., New York, and Dr. J. S. L. Browne, F.A.C.P., Montreal, Can., were among the speakers at a Symposium on Protein Metabolism, held Oct. 30, at the University of Toronto. Their respective subjects were "Amino Acids and Proteins in Therapy" and "Adrenals and Protein Metabolism." Dr. W. H. Sebrell, Jr., F.A.C.P., Bethesda, Md., presided over the afternoon session at which Drs. Pollack and Browne spoke. The Symposium, made possible by a grant from The National Vitamin Foundation, was sponsored by the School of Graduate Studies and the Department of Public Health Nutrition of the University of Toronto.

Under the Presidency of Dr. Oscar A. Sander, F.A.C.P., Milwaukee, the Wisconsin Chapter of the American College of Chest Physicians held its annual meeting, Oct. 4, in Milwaukee. Out-of-state speakers included Dr. George A. Hellmuth, F.A.C.P., Chicago, who discussed "Electrocardiographic Problems in Daily Practice," and Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., who spoke on "Palliative Treatment of Inoperable Bronchogenic Carcinoma." Local speakers included Dr. Joseph M. Lubitz, F.A.C.P., and Dr. Ray L. Rice, F.A.C.P., whose respective topics were "Granulomatous Lung Disease" and "Clinical Application of Ballistocardiography."

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, speaking on "The Hemodynamics of Valvular Lesions," was among the guests of the Oneida County Tuberculosis and Health Association when the society held its "Heart Day" in Utica, N. Y., Oct. 15. Dr. Arthur M. Master, F.A.C.P., New York City, discussed "Coronary Artery Disease and Treatment" and Dr. O. Henry Janton, Jr. (Associate), Philadelphia, gave "A Review of the Present Status of Cardiac Surgery." Dr. Simon Dack, F.A.C.P., New York City, presided at the evening session.

Dr. Robert L. King, F.A.C.P., Seattle, Wash., extended "Greetings from the President of the American Heart Association" to the San Francisco Heart Association at its annual Symposium on Heart Disease, held Oct. 28–30. Other out-of-state speakers and their presentations included Dr. Robert H. Bayley, F.A.C.P., Oklahoma City, "Possible Clinical Applications of Vectorcardiography"; Dr. Howard B. Sprague, F.A.C.P., Boston, "Uses and Limitations of Ballistocardiography"; Dr. Herrman L. Blumgart, F.A.C.P., Boston, "Pathology and Clinical Classification of Cardiac Pain," and Dr. Eugene A. Stead, Jr., F.A.C.P., Durham, N. C., "Present Views in Circulatory Failure."

Dr. Harold G. Wolff, F.A.C.P., New York, delivered the first lecture of the Fourth Annual Lecture Series sponsored by the North Shore Health Resort, Winnetka, Ill. The theme of the series is "Treatment in Psychiatry." Dr. Wolff's talk, given Oct. 7, was on "The Problem of Psychiatric Referral."

Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., President of the American College of Chest Physicians, was the principal guest speaker at a joint meeting of its Illinois Chapter and the Eighth Annual Postgraduate Course on Diseases of the Chest, held

in Chicago, Oct. 1. Drs. Alvan L. Barach, F.A.C.P., New York, Benjamin M. Gasul, F.A.C.P., Chicago, and Harold G. Trimble, F.A.C.P., Oakland, were among the participants in an X-Ray Symposium.

Dr. Israel Davidsohn, F.A.C.P., Chicago, acted as moderator of a panel discussion on "Training of Residents in Clinical Pathology," held during the annual meeting of the College of American Pathologists in Chicago, Oct. 12–13.

Drs. Irving S. Wright, F.A.C.P., College Governor for Eastern New York, Charles K. Friedberg, F.A.C.P., New York City, and Paul D. White, F.A.C.P., Boston, were speakers on the Annual Seminar in Postgraduate Medicine, sponsored by the Philadelphia Academy of General Practice and held in Philadelphia, Oct. 28.

Dr. White also addressed the Fifth Annual Meeting of the West Virginia Heart Association, Charleston, Nov. 6. Dr. White's topic was "The Changing Scene—New Hope for Hearts." Dr. Walter C. Swann, F.A.C.P., Huntington, was installed as President.

Using "Allergy in General Practice" as his theme, Dr. George Piness, F.A.C.P., Los Angeles, addressed a meeting of the New Jersey Allergy Society, held in conjunction with the Academy of Medicine of New Jersey at Newark on Oct. 15.

Dr. Hugh R. Leavell, F.A.C.P., Professor of Public Health Practice, Harvard University, Boston, was among the guest speakers at the 25th anniversary celebration of the Columbia-Presbyterian Medical Center, held in New York City, Oct. 12–13. Dr. Robert F. Loeb, F.A.C.P., New York, Executive Officer of the Department of Medicine, read a paper entitled "Role of the Internist in Medicine Tomorrow."

Dr. William A. Sodeman, F.A.C.P., formerly Professor of Preventive Tropical and Semitropical Diseases and Hygiene at Tulane University of Louisiana School of Medicine, has been appointed Chairman of the Department of Medicine at the University of Missouri School of Medicine, Columbia.

Dr. John A. Schindler, F.A.C.P., Monroe, has recently been appointed by Governor Walter A. Kohler to the Wisconsin State Board of Medical Examiners.

Dr. Edwin J. Rose, F.A.C.P., took over his duties Sept. 8 as Manager of the Mount Alto Veterans Administration Hospital, Washington, D. C. Dr. Rose was formerly Assistant Director, Hospital Operations Service, Veterans Administration Central Office.

At the University of Wisconsin Medical School, Madison, Drs. Edgar S. Gordon, F.A.C.P., and Marc J. Musser, Jr., F.A.C.P., have been promoted to Professors in the Department of Medicine, and Dr. John LeRoy Sims, F.A.C.P., has been advanced to Associate Professor.

Colonel Robert B. Skinner, M.C., F.A.C.P., formerly Deputy Commander of Letterman Army Hospital, San Francisco, California has recently been assigned as Commanding Officer, United States Army Hospital, Fort Dix, New Jersey.

Dr. Hobart A. Reimann, F.A.C.P., presently Professor of Medicine at the American University of Beirut, Beirut, Lebanon, participated in the Fourth International Congress on Tropical Medicine in Istanbul, and with Dr. Zellweger, presented a paper before the Fourth Congress for the Study of Biologic Rhythms in Basle during September.

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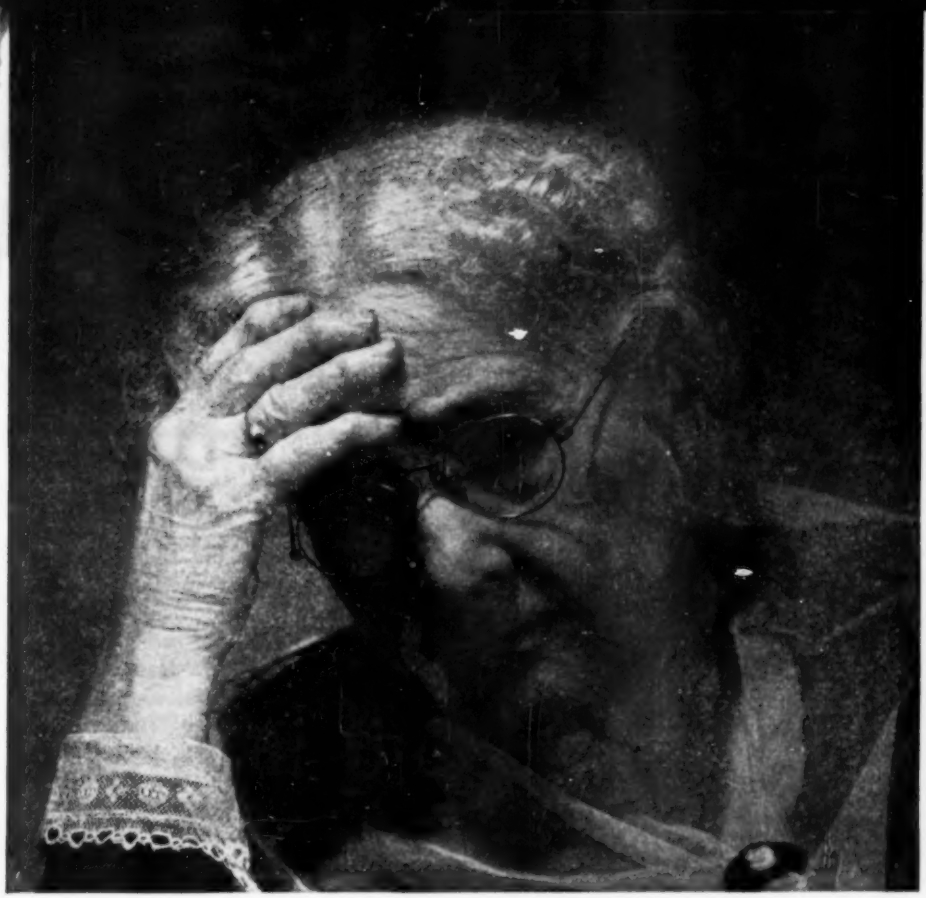

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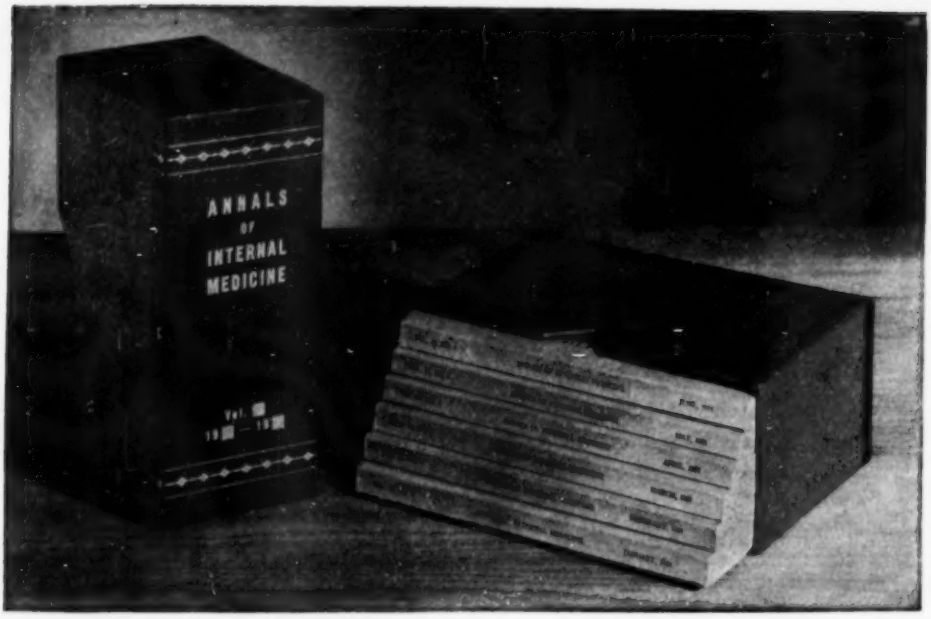

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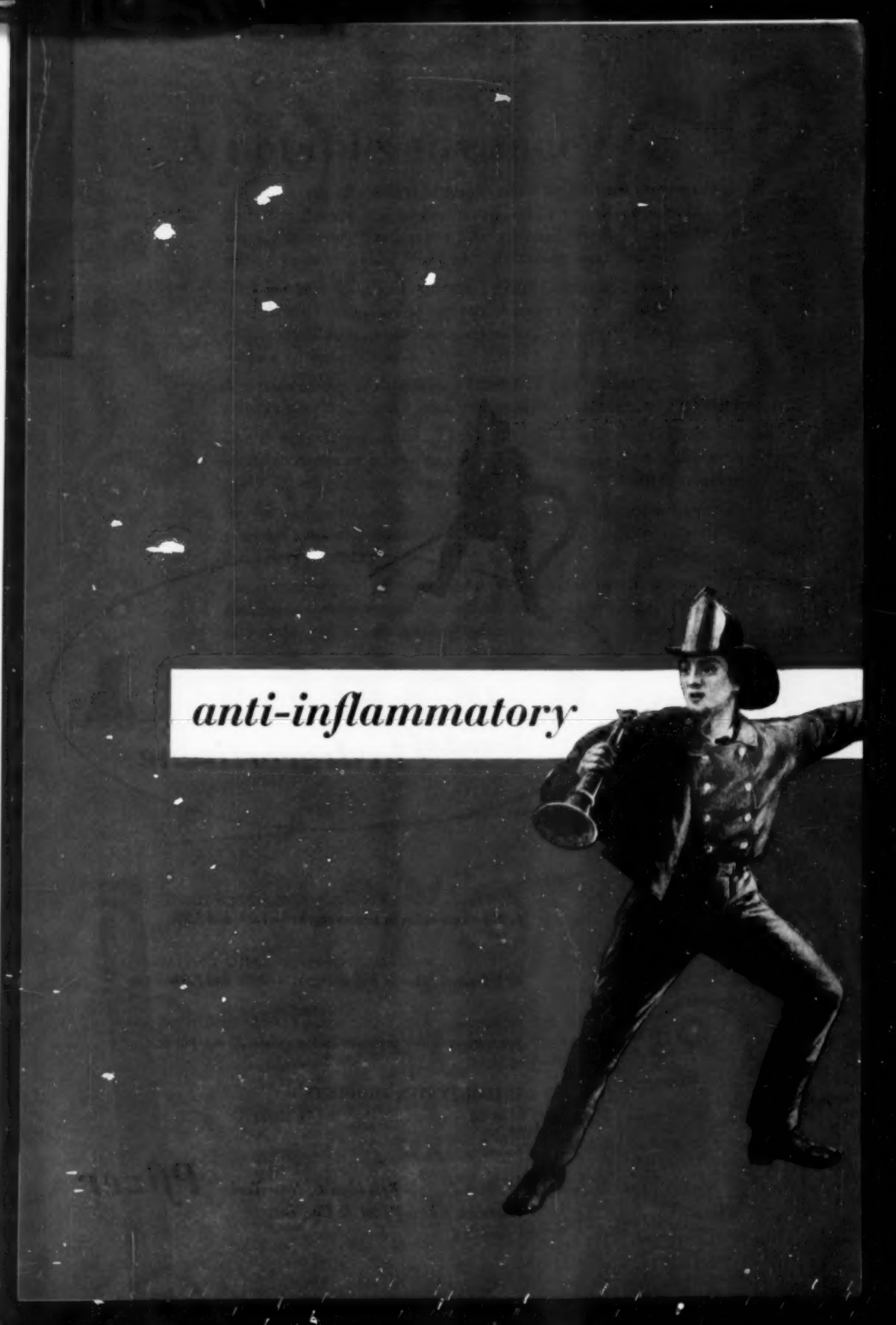
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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952.
3. Perlman, A.: Angiology 3:16 (Feb.) 1952.

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CHICAGO, ILLINOIS, APRIL 5–9, 1954

General Headquarters, Meetings and Registration—Conrad Hilton Hotel.

Hotel Headquarters, Conrad Hilton Hotel. Hotel reservation forms will be provided when the program is distributed in February, 1954. Physicians and exhibitors may apply directly to any hotel of their choice.

Technical Exhibit—Exhibition Hall, Conrad Hilton Hotel. 133 booths. Exhibitors limited to those on Invitation List. Exhibits restricted to products relevant to the practice of Internal Medicine or its allied specialties. Preference given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books. All exhibits must be approved by the Committee on Exhibits.

Meetings—all to be held at Conrad Hilton Hotel.

Program—will appear in the February, 1954, issue of this journal, and will be printed separately and distributed to all members of the American College of Physicians and non-member physicians whose names are on the mailing list. Program will consist of General Scientific Sessions, Symposia, Color Televised Clinics, Panel Discussions and Clinical-Pathological Conferences. Speakers and participants will be carefully selected authorities in the several fields of Internal Medicine and allied specialties, including Pediatrics, Dermatology, etc.

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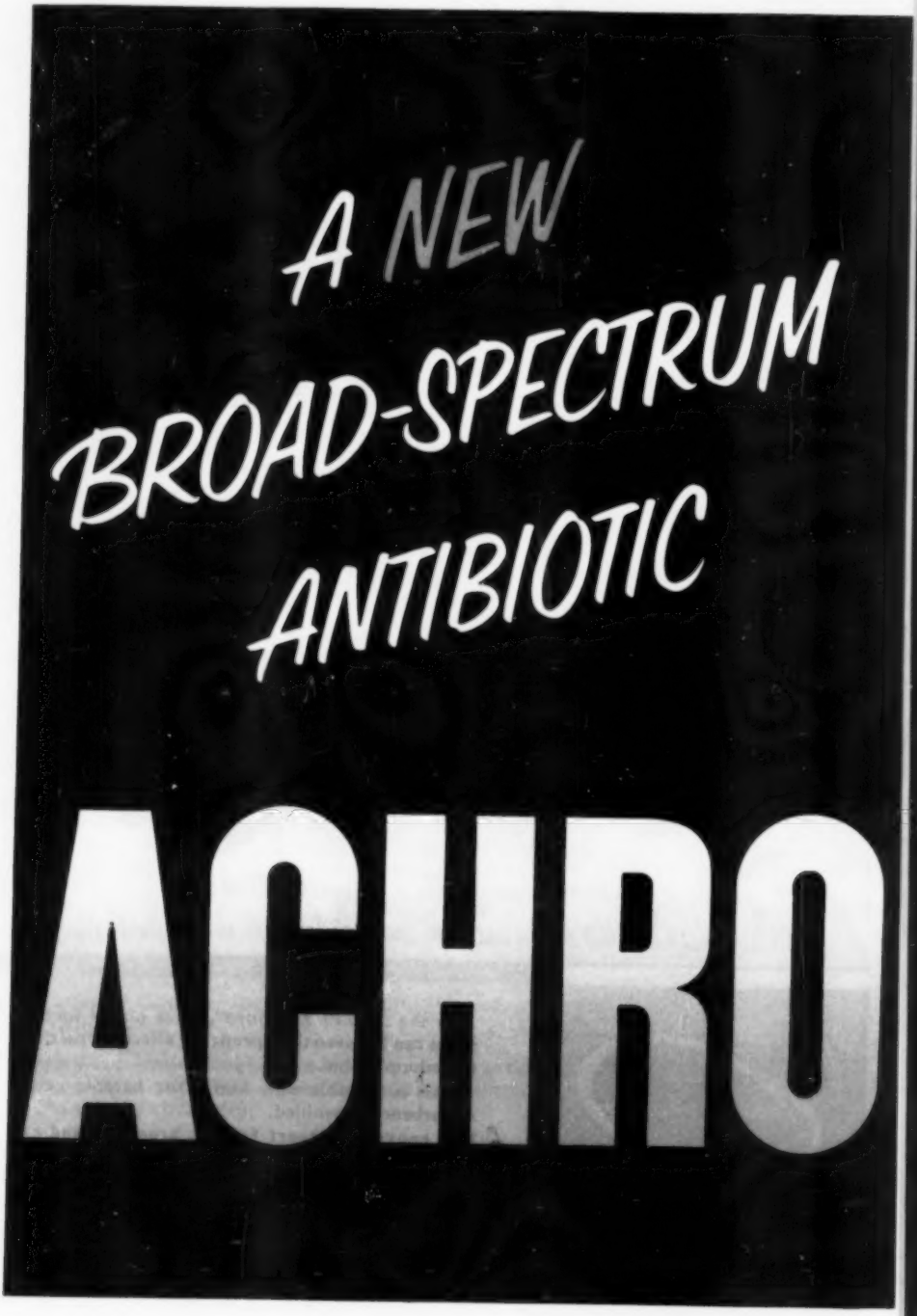
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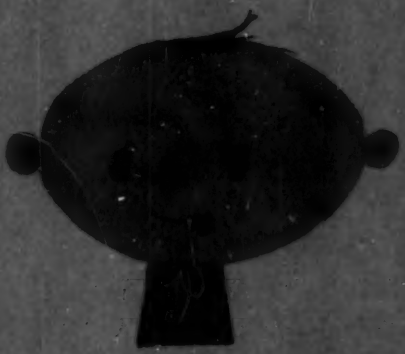

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